The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 7 MARCH, 1947 NUMBER 3
Copyright 1947 by the Association for the Study of Internal Secretions

THE CONSTITUTIONAL TYPE OF PRECOCIOUS PUBERTY

A. M. HAIN

Institute of Animal Genetics, Edinburgh University, and Royal College of Physicians' Laboratory, Edinburgh

"CONSTITUTIONAL" is the term used by Novak (28) to describe a type of precocious puberty for which no adequate cause has yet been found. This does not mean that a pathologic condition may not exist but that all the known conditions associated with sexual precocity have been excluded in the cases in question. Such conditions are the following:

(a) Granulosa-cell tumor of which there have been fully sixteen instances of its association with precocious puberty, Novak (28); three of these are described by Novak (27). An interesting observation made by this author (28) is that menstruation in such individuals, being of the estrogen-induced type is always anovulatory, which is in contrast with that of the so-called "constitutional" type; in one of the children to be described later on, pregnanediol was being excreted, showing that ovulation had occurred.

(b) Sexual precocity of the cerebral type has been recorded in seventeen cases (Weinberger and Grant (37)) in all of which lesions of the hypothalamus and third ventricle were present; girls are rarely affected with this lesion, though cases have been recorded by Dott (8), Bing, et al., (2) and by Gross (13) (his case 7). Ford and Guild (11) describe precocious puberty in two girls, aged 9, following measles encephalomyelitis and in a boy, aged 11, following epidemic encephalitis. These authors give a useful review of precocity due to brain tumors and add 7 cases to be ascribed to hypothalamic lesions caused by inflammatory processes; furthermore it is well

recognized that in cases of hydrocephalus a degree of sexual precocity frequently exists. Pineal tumors have been held to cause precocious puberty in boys but the sum of evidence to date (31) not only shows that the pineal gland is not a secretory structure but that the tumors in this region produced their effects either by their nature, e.g., as embryonal tumors, teratomas or mixed tumors or by their pressure effects on the hypothalamus or its nervous connections.

(c) In cases of sexual precocity one must also consider the possibility of adrenal cortical involvement, chiefly suspect in the sexually precocious *boy*. In a girl, hyperfunction of the adrenal cortex is almost always accompanied by virilism: hirsutism, deep voice, boyish figure and clitoris enlargement, but seventeen cases are on record in which menstruation has either preceded or occurred simultaneously with symptoms of heterosexual precocity. Halban (16) cites seven of these cases in all of which adrenal tumors were verified by autopsy; these and the remaining ten cases are referred to in the following table:

TABLE I. THE ASSOCIATION OF MENSTRUATION WITH ADRENAL TUMORS IN CHILDREN

Author	Age of child	Remarks
Mathias	3 years	Repeated menstrual periods.
Eigen	9 years	Menstruated once.
Bulloch and Sequeira	11 years	Menstruation and marked mammary development.
Schmidt	?	Menstruated once.
Lesser (25)	3 years	Menstruation followed by mammary enlargement.
Cooke (5)	7 years	Menstruation aet. 4–7 years.
Kayne et al. (20) (cited by Halban (16)	7 years	Menstruation before virilism.
Walters et al. (35) (Case 2)	8 years	
Lasné	9 years	
(Riche	3.9/12 years	Aberrant adrenal tumors
Gaudier (cited by Reilly et al. (30)	4 years	attached to the ovary.
Hoag (19)	10 years	Only case out of 22 with hypernephroma.
Knewitz (22)	2 years	Adenocarcinoma found at aet. 5 years.
Freedman (12)	6 months	Menstruation and hirsutism.
Kepler et al. (21)	19 months	Menstruation followed by virilism
Harvey (18)	2½ years	Regular menstruation for 9 months, due to large cellular sarcoma of left kidney and adrenal.
Walters and Kepler (34)	2 years	2 or 3 menstrual periods.

In the majority of these patients hirsutism was present (or developed) and there was enlargement of the clitoris. Three of those enumerated are of special interest because menstruation and breast enlargement *preceded* development of any symptoms of virilism:

(i) Kayne et al. (20): menstruation in a girl aged 7 years was followed by amenorrhoea and the adoption of the male habitus with enlargement of the clitoris.

(ii) Lesser (25) is cited by Danforth (7) as describing a similar case; menstruation followed breast development when the child was 2 years old and lasted till 3½ years, when it ceased and hairiness developed so that at 6 years the child had a definite moustache and beard. At least one of the ovaries was enlarged.

(iii) Kepler et al. (21): menstruation and breast enlargement occurred in an infant of 19 months, who later developed symptoms of virilism and from whom an adrenal cortical carcinoma weighing 45 grams was subsequently removed. This sequence of events is probably of very rare occurrence.

(d) The gonadal group is the largest, as, in 21 out of 25 cases of precocious menstruation reviewed by Elterich (9), tumors or cysts of the ovaries were found, at operation or autopsy, and in 13 of these cases the tumor was of the nature of a sarcoma. To Elterich's total may be added the case of Fischer (10) in which menstruation in a child of 4½ years was associated with a cystic mass in the ovary with luteinization of the theca. Prior to operation the child excreted 31 mg. of sodium pregnanediol glucuronide which is equal to the amount excreted by a 5 months' pregnant woman. Elterich (9) encountered only one instance of "natural" or "constitutional" precocity—a girl aged 4 years; Novak (28) reports 9 cases of his own, Werner (38) two and Craven (6) one. With the possible exception of one case described by Young (39) (chap. 12) the author is not aware of any instance or precocity of this type in *boys;* two such are described in this report. At 4 years of age Professor Young's patient was 10 in. taller and 27 lb. heavier than a normal boy of his age; his muscular development was remarkable and sexual development was equal to that of an adult. Intellectually he was retarded, being equal to a 3 year old boy. Epiphyseal development was similar to that of a boy 10 years old. No pathologic condition was found at laparotomy, though the left adrenal was slightly larger than the right. It was not so large as the adrenal at birth and no part of it was removed. At that time estimation of the excretion of 17-ketosteroids was not a routine procedure for measurement of adrenal cortical function so that the possibility of cortical hyperplasia being the underlying cause of the precocity is not excluded, though such cases are exceedingly rare in boys, in spite of their relatively frequent occurrence in girls. This boy grew 6 in.

in 3 years (slower than the normal rate) and only ½ in. during the fourth year. At 8 he was stronger than a youth of 16.

The accelerated skeletal development described in the foregoing case is a characteristic of precocious puberty. According to Elterich (9), St. Hilaire was the first to call attention to it, and Lenz (24) found that osseous union of the epiphyses and diaphyses, normally occurring at the end of the second decade, was already complete in a 6 year old girl and the skeleton equal to one of 18 years. The pelvis in many cases resembles that of a fully developed female. Though at first taller than normal for their age, such patients are finally below the average height and even dwarf-like in appearance, owing to an early cessation of growth caused by premature ossification of the epiphyseal cartilages. This macrogenitosomia is not confined to isosexual precocity and, indeed, is even more marked in cases of adrenal cortical hyperfunction (whether due to tumor or hyperplasia of the cortex) in which heterosexual precocity occurs in the female child. This acceleration of osseous development occurs also in cases in which no adrenal involvement can be demonstrated, e.g., in precocity due to brain tumors and to ovarian and testicular tumors. It seems likely that the condition is caused by an interaction of adrenal, gonad and pituitary linked up with the metabolic processes.

Reference has been made to the fact that girls with the "constitutional" type of sexual precocity ovulate, whereas those in whom the condition is attributable to granulosa-cell tumor do not. Novak (28) found indubitable evidence of ovulation in three of his patients in whom corpora lutea were found at laparotomy. Further evidence of ovulation is provided by the fact that pregnancy has occurred in several cases of this kind. Elterich (9) counted 30 below 12 years old, children being born to mothers aged $5\frac{8}{12}$ years, 6 years (2 cases) and 9 years (cited by Novak (28). This fact, together with the report that no lesion manifested itself in the later life of the patient (a normal menopause at 52 years is reported in one of the cases) (24), is strong suggestive evidence that the condition is a premature development of a normal process.

(e) A fifth series of cases of sexual precocity is that described by McCune (26) in which the condition was associated with bone cysts and pigmented nevi (xanthomatosis?). McCune described one such case, a girl aged 9 years, and Dr. Albright added thereto five similar cases in which menstruation started at 1, 7, 3, 4 and 7 years respectively. It was suggested that the association of the condition with precocious puberty might be due to the disturbance in cholesterol metabolism which occurs in xanthomatosis, cholesterol being a lipoid chemically not very different from estrogen. Might it not be, however, that these bone cysts were those associated with a Hand-Schüller syndrome and that pressure on the hypothalamus had

given rise to sexual precocity instead of inducing the exophthalmos and diabetes insipidus usually found in this condition?

These 5 groups comprise the generally accepted causes of sexual precocity other than that of the "constitutional" type, which, in spite of the absence of controlled data regarding the gonadotropin excretion, has generally been attributed to "hyperpituitarism." A brief review of hormone excretion reported in the various types of sexual precocity will show how these may be differentiated, and will illustrate how little positive information has hitherto existed in the case of "constitutional "precocity.

McClune (26), in reporting his case, remarks that in addition to estrogen, which varied from 5–95 rat units per litre of urine, gonadotropin "was present periodically." In only one of Novak's (28) cases was the gonadotropin excretion estimated; Case 1 excreted "small amounts" of gonadotropin, while the estrogen excretion varied from less than 3 and 4 rat units to 20–25 rat units per litre. In five cases Novak observed that one ovary was enlarged and in almost every case the portion removed for biopsy contained small cysts and a retrogressing corpus luteum just below the surface. Allen (1) in Chap. 23 remarks—"Female infants with precocious puberty reveal in assay tests an amount of follicular hormone closely approximating that found in post-puberal girls." Menstruation due to granulosa-cell tumor is associated with very high values of estrogen excretion; those collected from the literature by Palmer (29) ranged from 65 M.U./litre to 17,390 M.U./litre, and the author recently recovered in one case >1200 I.U./litre. It should be noted, however, that Gross (13) reported values for estrogen equal to 175–650 I.U./24 hours in a child aged 2 years in whom menstruation proved to be due to an "astrocytic hamartoma" in the hypothalamus. Kraus (23) found an increased prolan excretion in 60 per cent of the patients with cerebral tumors. Teratomas and some testicular tumors are also associated with an exceedingly high gonadotropin output. Precocity (whether isosexual or heterosexual) due to tumor or hyperplasia of the adrenal cortex is associated with high 17-ketosteroids excretion—values ranging from 20 to 300 mg./24 hours—and sometimes also with the excretion of considerable amounts of pregnanediol (14). Only one instance of the excretion of the latter is recorded in a case of precocious menstruation due to a luteal cyst (10): a child aged 4½ years who menstruated every 3 months from the age of 3 years and who was excreting 31 mg. sodium pregnanediol glucuronide daily.

METHODS

The following were used for hormone analysis:—

17-ketosteroids: Patterson's method, described by Hain (14).

Gonadotropin: a modification of Scott's kaolin adsorption method, described by Hain (14).

Pregnanediol: Venning's method (33).

Estrogen (combined): hydrolysis extraction by method I of Callow et al., (4), fractionation by their Method II; biological assay as performed by Hain and Robson (15).

DESCRIPTION OF CASES

Case 1. (Record P409—Dr. Clifford Kennedy's patient)—A girl, aged 4 years, was admitted to the hospital Sept. 1943. Vaginal bleeding (a few spots) started when she was only 3 months old, and occurred again in Nov. and Dec. 1939. Bleeding occurred twice in 1940, 5 times in 1942, on each occasion a trace for approximately 4 days. A month before entering the hospital there was some vaginal bleeding for 7 days. On examination the patient was very well developed; mammary tissue and external genitalia were developed in advance of her age and the hymen was ruptured. She was mentally alert, with the reasoning power of a child of 7 or 8 years; a wayward and difficult child, she took several days to settle down in the ward. Height 45″, weight 43½ lb., B.P. 85/60, r.b.c. 4.5 mill., w.b.c. 10,900, Hb. 89%, urea N 10 mg. %, Tot. protein 6.58 gm.%. Ossification = 6–9 years, development = 17 years; sella turcica normal. Hormone findings per 24 hours:

	17-keto-steroids	*sod. pregdl. gluc.*	*estrogen*	*A. Z. test*	*gonadotropin*
1943 (Sept.)	2 mg.	a trace	(free) 200 I. U.	not done	not done
1944 (Oct.)	3 mg.	4 mg.	(combined) <4 I. U.	negative	not done
1945 (July)	1.4 mg.	not done	not done	not done	16 M.U.

The ketosteroid output was only slightly raised, being equal to that of a girl of 6 or 7 years; the excretion of 4 mg. sodium pregnanediol glucuronide on the 12th day of a menstrual cycle indicated some luteal activity. On account of the high output of estrogen in 1943 an ovarian tumor was suspected and Dr. Kennedy was asked to explore the abdomen. The left ovary was larger than the right and on removal was found to contain follicles in all stages of development, and 2 atretic follicles, but no evidence of granulosa cell tumor formation.

There was no further menstruation, after this operation, for a whole year. Menstruation, lasting about 4 days, occurred in Sept. and Oct. 1944 and twice in March 1945 which is the last period for which we have data of the case. After the operation the child improved immensely and was much more amenable. There was no regression in her breast development during the two years following.

The amount of gonadotropin excreted by this patient—16 M.U./24 hrs.—is as much as an adult woman excretes; children of even 7 and 8 years of age do not excrete more than 4 or 5 M.U./24 hrs. It is interesting that this amount was being excreted 4 months after the last menstruation. It would seem that the initial stimulus which had started the menstrual rhythm (and also, presumably, pituitary secretion) was sufficient to maintain secretion at an adult level. The absence of menstruation may have been due to pituitary secretion not rising to high enough values.

Case 2. (Record P478—Mr. Broster's patient)—A girl, aged 3 years 7 months entered the hospital in Feb. 1944. White vaginal discharge when 1 month old; breasts prominent almost from birth; menstruation started at 19 months and occurred every 5 weeks lasting 4 days. Progesterone, injected at 2 years old, stopped periods for 6

months. Pubic hair at 2 months; had 18 teeth by 18 months, anterior fontanelle closed at 1 year; walked at 7 months, talked at 8 months. In an intelligence test when just 2 years old she was graded as 4½ years. Weight at 2 years 42 pounds; at 3 years 7 months 49 pounds, height 3′6″.

Hormone finding per 24 hours:

	17-ketosteroids	*pregnanediol*	*estrogen (combined)*	*A. Z. test (double amount)*
Jan. 27, 1944	2.8 mg. (5.6 mg./litre)	a mere trace	<4 I. U.	completely negative
Feb. 18, 1944	2.4 mg. (4.0 mg./litre)			

At operation on March 3, 1944, the left ovary consisted of a large blood cyst about 1″×2″ with a small amount of normal ovarian tissue. The right ovary—about ½″×1″ was enlarged and contained a small blood cyst. Both adrenals were enlarged and granular. The uterus was larger than normal for her age. Her epiphyseal age was 12 years, but her teeth age was less than 6 (incisors not erupted). A scanty menstruation occurred 4 days after the operation. No note of this patient's gonadotropin excretion is available as this analysis was not being performed in 1944.

Case 3. (Record P498—Dr. Weiner's patient)—A girl aged 9 years 7 months, was admitted to Leeds General Infirmary March 1944 with a history that she had begun to menstruate at 8 years, had had 4 periods in the past 12 months and 2 during March 1944. There was nocturnal and diurnal enuresis. Two sisters aged 13 and 5 years respectively were quite normal. Axillary and pubic hair was present and breasts were greatly enlarged. Striae also were visible and there was impaired sugar tolerance. B.P. 125/95 to 100/55; r.b.s. 4.5 mill.; generalized obesity (91 lb., abdomen 30″). Height 51½″, chest 32″, length of lower half of body 26½″. At X-ray her carpal centres were equal to those of a child 12 years old.

Hormone findings per 24 hours:

	17-ketosteroids	*pregnanediol*	*estrogen (combined)*	*gonadotropin*
Apr. 1944	3.0 mg. (i.e. 8.5 mg./litre) 3.4 mg.	"pregnane derivative"	<5 I. U.	not done
Apr. 1945	3.4 mg. (i.e. 6.8 mg./litre)	not done	not done	25 M.U.

The ketosteroids output was not above the average for a child of 9–10 years of age. Talbot et al. (1940) give the average excretion at 7–12 years as 4.0 mg./24 hrs.; the author's figure for girls aged 8–9 years is 2–3 mg./24 hrs. or 3.5–6.6 mg./litre.

The recovery of a "pregnane derivative" instead of pregnanediol in the acetone fractions of Venning's method has been reported by the author (14) in a case of adrenal cortical carcinoma when the patient was dying and has been encountered by her in a few women with virilism, in mastitis and in gynecomastia in men. The only other child in whom it has been recovered was K195, a female aged 16 months who had an enlarged clitoris and pubic hair, and who excreted 6.25 mg. 17-ketosteroids per litre. In case 3 "pregnane derivative" was recovered on the sixth day after menstruation began.

The excretion of 25 M.U. gonadotropin/24 hours in a child 10½ years old is definitely abnormal and represents the output of a normal adult. Unfortunately the stage of the

menstrual cycle at the time was not known. The impaired sugar tolerance, striae and enuresis are features suggestive of possible hypothalamic disturbance requiring this case to be put in a different category from the others in this series.

Case 4. (Record K172—Dr. J. B. Donald's patient)—A girl, aged 11 years, was admitted to the hospital Feb. 1946 on account of marked breast development and a history of having menstruated 3 weeks previously. Novak (28) considers that 8 or 9 years should be taken as the limit of "precocity" and that maturation after these years is within the limits of normality. This figure would be considered much too low for this country, 11–12 years being probably the lowest normal, so that possibly in the case of K172 the beginning of sexual development was not so accelerated as to be beyond normal limits. Patient's weight was 67 lb., height 52″, span 49″.

Hormone findings per 24 hours:

17-ketosteroids	*pregnanediol*	*gonadotropin*	*estrogen*	*A. Z. test*
4.4 mg. (i.e. 3.5 mg./litre)	slight trace	12 M.U.	<10 I. U.	negative

The ketosteroids output was normal; gonadotropin output was probably slightly in excess of the average for a girl of 11 but no data are available at present; the low estrogen excretion and negative A. Z. test excluded granulosa-cell tumor and embryonic or brain tumors as the underlying cause of the condition.

Case 5. (Record K158—Dr. R. B. Magill's patient)—A girl, aged 6½ years, developed normally until the last 6 months during which there had been excessive body-growth, accompanied by marked enlargement of the breasts. There was scanty pubic hair. Menstruation occurred in Nov. 1945 and Jan. 1946, just prior to consulting Dr. Magill. Patient has a sister aged 18 in whom menarche occurred at 14 years. On examination the uterus was found equal to that of a girl of 17, but the ovaries were small; the clitoris was normal. X-ray revealed no abnormality in the region of the pituitary; age of hands = 8 years; weight 57 lb., height 45½″, span 47½″. (Photo: Fig. 1.)

Hormone findings per 24 hours.

	17-ketosteroids	*pregnanediol*	*gonadotropin*	*A. Z. test*
Jan. 16, 1946	4.1 mg. (14.1 mg./litre)			completely
Jan. 28, 1946	5.0 mg. (6.9 mg./litre)	none	8 M.U.	negative

The ketosteroids are slightly higher than average for her age; so also is the gonadotropin output (which was taken on the 20th day from the start of a menstrual period lasting 7 days). Estrogen excretion was not ascertained directly but an excess such as accompanies granulosa-cell tumor would have shown itself in the A. Z. test, which proved completely negative.

An interesting fact regarding this child's mother was elicited by Dr. Magill: after the birth of the first girl she had two miscarriages due to fibroids for which an operation was performed 1½ years before the birth of the patient. The possibility that an abnormally high estrogen secretion (which, presumably, gave rise to the fibroids) had affected the fetus ante-natally, suggests itself. The length of the interval that elapsed in this case before any symptoms became manifest is difficult to explain, and such an explanation would seem more feasible in those cases in which vaginal bleeding commenced during the first year. It is possible, however, that a centre is stimulated which requires a certain period to elapse for its full function. The matter is discussed again later.

To this series of girls may be added three in whom precocious development was unaccompanied by menstruation; they are under the care of Dr. Douglas Nicholson and Dr. R. A. Miller who are working for the Department of Child Life and Health, Edinburgh:—

K294—aged 10, = 14 in development; normal till appendectomy at age 8 when she began to put on weight; wt. 90 lb., ht. 53″, abdomen 31″, legs only 24½″; B.P. 110/65.
K312—aged 8$\frac{11}{12}$ yrs., ht. 60″, wt. 92½ lb., abdomen 29″, legs long, proportions almost adult; mammae and limbs = 11 yrs. in development.
K317—aged 9$\frac{11}{12}$ yrs., measurements and weight normal: 63¾ lb., also B.P. 120/65,

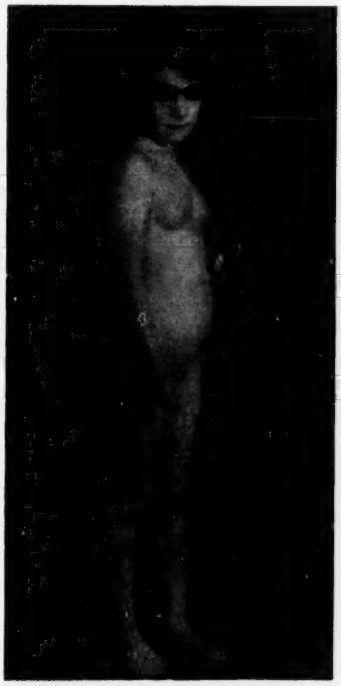

FIG. 1. Case 5—Dr. McGill's patient: age 6½ years.

but "developing too quickly": pubic hair for 1 year, axillary hair for 6 months, breasts slightly enlarged.

Hormone findings of these three girls, per 24 hrs.:

case no.	*17-ketosteroids*	*gonadotropin*
K294	4.8 mg. (i.e. 10 mg./litre)	22 M.U. (i.e. 45 M.U./litre)
K312	2.2 mg. (i.e. 5 mg./litre)	7 M.U. (i.e. 15 M.U./litre)
K317	5 8 mg. (i.e. 10.5 mg./litre)	13 M.U. (i.e. 25 M.U./litre)

The secretion of gonadotropin is definitely higher than is normal for this age in K294 and K317 and probably also in K312, and justifies placing these patients in the category of the sexually precocious of "constitutional" type. All cases of this type should be observed periodically.

Only two boys with sexual precocity of the "constitutional" type have been encountered:

Case 6. (Record P519—Dr. Vining's patient)—Boy, aged 5 years, was admitted to Leeds General Infirmary Sept. 1944: 10″ above average height, testes and penis = 15–17 years; pubic hair present; B.P. 105/75. Testicular biopsis revealed no interstitial cell hyperplasia but seminiferous tubules were almost adult in appearance and spermatozoa heads were seen in several tubules.

Hormone findings per 24 hours:

17-ketosteroids	*pregnanediol*	*gonadotropin*	*estrogen*	*A. Z. test*
2.25 and 5.0 mg.	"pregnane derivative"	17 M.U.	<10 I. U.	negative (also with 5.0 cc. urine)

As in other cases reported in this study the 17-ketosteroids are only slightly above the average for the age of the patient. The figure given by Talbot et al. (32) for children of 4–7 years is 1.3 mg./24 hrs., but the author has records of normal girls at 5–6 years of age excreting 2.0 to 2.5 mg./24 hrs. Boys tend to excrete slightly higher values than girls of the same age.

The excretion of 17 M.U. gonadotropin/24 hrs. is on a par with the adult values obtained in the other members of this series of "precocious" children. Normal children of the same age excrete from <2 to 4 M.U./24 hrs.

Case 7. (Record K263—Dr. J. B. Donald's and Mr. G. L. Alexander's patient)—A boy aged 6½ years, height 4′5″, weight 44 pounds, well-developed and proportionate; adult genitalia, axillary and pubic hair well-grown; mustache beginning. Voice broke at 4½ years, now baritone. Adolescent acne since 4½ years. Ossification = boy of 14 years; no skeletal deformity. Sella turcica not enlarged; no polydipsia or polyuria. Nothing abnormal in mother's or family's history. (Photo: Fig. 2.)

17-ketosteroids	*gonadotropin*	*A. Z. test*	*5.0 cc. urine per immature mouse*
6.0 mg.	18 M.U.	completely negative	no effect

Again the 17-ketosteroid excretion was slightly above normal; it was in keeping with his precociously mature condition, as was also the gonadotropin output, similar values having been obtained by the author in a normal boy of 14. The absence of any reaction in the A. Z. test and when 5.0 cc. of urine was injected, indicated that there was neither a testicular nor an embryonic tumor to account for the precocity.

DISCUSSION

Hormonally all the members of this group of cases have in common an excretion of gonadotropin such as is found only after puberty; the values recovered were 16, 25, 12, 8, 22, 7, 13, 17, and 18 M.U./24 hrs. In addition the excretion of 17-ketosteroids was above the average for the age of the patient, but well below values associated with hyperplasia or hyperfunction

of the adrenal cortex, conditions which are associated with an excretion of 20–300 mg./24 hrs. It is likely that, in such patients, pituitary function as a whole is at an increased rate so that not only is gonadotropin secretion in excess of normal but also the secretion of corticotropic hormone; thus the adrenal cortex participates in the precocious maturation which the gonads display. In the two boys that have been included in the series, a

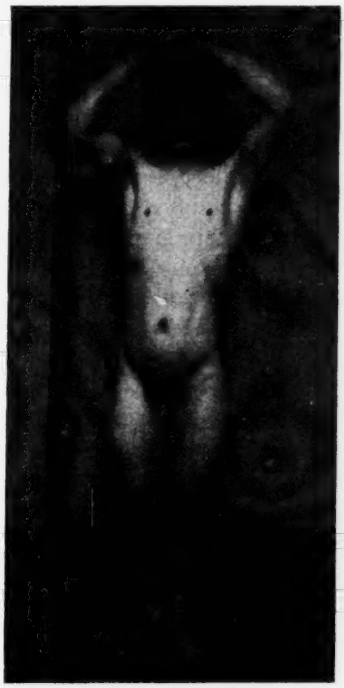

FIG. 2. Case 7—Dr. Donald's and Mr. Alexander's patient: age 6½ years.

little of the androgen may have come from testicular function as the gonads were mature in each case.

The absence of any history of illness which would be likely to affect the brain and ultimately the pituitary, by way of the hypothalamic centres, taken in conjunction with the only slightly raised excretion of gonadotropin, makes it highly improbable that there was any pituitary overactivity due to chronic increased intracranial pressure. The urine of such patients, according to Kraus (23), is so rich in follicle-stimulating hormone that only 3.0 cc. causes follicle-ripening when injected into immature mice. In every one of our cases this amount was completely ineffective.

The fact that in so many cases precocious menstruation has been followed by normal function throughout life and that there have been thirty instances of motherhood at 12 years of age and under (9) demonstrates that such an occurrence is not necessarily pathologic. It is of the greatest importance to differentiate, by hormone assays, between the pathologic and the merely "precocious" condition.

As to why an otherwise normal mechanism should be awakened at an abnormally early age, no satisfactory explanation seems forthcoming. Novak (28) assumes a chromosomal or genic basis as the most plausible, hence his term "constitutional." In one instance in our series—but alas! only one—a history of fibroids suggested the possibility of intrauterine action of estrogen upon the fetus. The delay in the manifestation of "precocity" has a counterpart in the delay in its occurrence after inflammatory processes in the brain, viz. 12, 7 and 8 years (11). It would seem that years elapse, after the initial stimulus is given to set en train the course of puberty, before outward signs become manifest.

Reference has been made to the recovery in two cases of a substance allied to pregnanediol (since it is obtained by the Venning method used for isolation of sodium pregnanediol glucuronide) which we have called a "pregnane derivative." Since the only occasion on which pregnanediol is excreted other than in pregnancy and the luteal phase of the menstrual cycle is in hyperplasia or tumor of the adrenal cortex, it seems likely that the "pregnane derivative" is the result of abnormal function of the adrenal cortex. It would be fallacious to argue that sexual precocity of the type herein described is due to abnormal adrenal function as it is quite possible that the latter is the result of the former. If, however, for purposes of argument, abnormal cortical function is taken for granted, its existence as the result of maternal hypersecretion of estrogen ante-natally is intelligible since estrogen does cause hypertrophy of the adrenal cortex (3). The suggestion need not be carried too far, as it is entirely a matter of speculation. The sequence of menstruation and adrenal cortical abnormality carries weight from the number of instances in which such abnormality has subsequently developed (see Table I.)

To describe cases of "constitutional" precocity as being due to "hyperpituitarism" is misleading. Such a term as "hyperpituitarism" is rightly applied to sexual precocity following on teratomas and cerebral tumors or inflammatory processes in the brain in which there has been destruction of structures which normally inhibit anterior pituitary activity through the hypothalamic channels. In such cases pituitary secretion is so excessive that either as little as 3.0 cc. of urine gives a positive A. Z. reaction (i.e. blood points in the ovaries of immature mice) or with 5.0 cc. of urine marked uterine enlargement is obtained, indicating the excretion of some

hundreds of Mouse Units of gonadotropin per 24 hours—a very abnormal condition. The cases that have been described in this report are examples in which a normal mechanism has been set in motion, but prematurely.

Novak (28) in reporting his cases makes certain wise recommendations: (a) to examine the patient at regular intervals, especially if no operation was performed; and (b) to stress the necessity for careful psychological management of such children, to avoid selfconsciousness in the child and a sense of inferiority or of abnormality, as well as to ensure protection against insemination.

SUMMARY

1. The various causes of sexual precocity are enumerated and the "constitutional" type is defined.

2. Five girls and two boys with sexual precocity of the "constitutional" type are described and their hormone output is given.

3. Excretion of gonadotropin and of 17-ketosteroids in excess of the normal for the age of the patients is common to all, the gonadotropin output being equal to that found in many adults.

4. In two cases a "pregnane derivative" was excreted instead of pregnanediol.

5. Possible reasons for the early awakening of a normal mechanism are discussed.

ACKNOWLEDGMENT

The investigation was performed during the tenure of the Kirk Duncanson Fellowship from the Royal College of Physicians, Edinburgh, for which the author expresses indebtedness. The author is also exceedingly grateful to Dr. J. B. Donald for helpful criticism of the manuscript.

REFERENCES

1. Allen, E., Danforth, C. H., and Doisy, E. A. *Sex and Internal Secretions* (2nd Edition). London, Baillière, Tindall and Cox, 1346 pp. (1939).
2. Bing, J. F., Globus, J. H., and Simon, H. Pubertas praecox: Survey of reported cases and verified anatomical findings, with particular reference to tumours of the pineal body. *J. Mt. Sinai Hosp.* **4**: 935–965 (March–April 1938).
3. Bourne, G., and Zuckerman, S. Changes in the adrenals in relation to the normal and artificial threshold of oestrous cycle in the rat. *J. Endocrinol.* **2**: 283–310 (Sept. 1941)
4. Callow, N. H., Callow, R. K., Emmens, C. W. and Stroud, S. W. Methods of extracting compounds related to the steroid hormones from human urine. *J. Endocrinol.* **1**: 76–98 (June 1939)
5. Cooke, W. Cited by Halban (16) (1925) and by Lenz (24) (1913). q.v.
6. Craven, J. D. Precocious Menstruation. *Am. J. Dis. Child.* **43**: 936–941 (April 1932).
7. Danforth, C. H. *Hair, with Special Reference to Hypertrichosis*, Chicago, Amer. Med. Assoc. (1925).

8. Dott, Norman M. From *The Hypothalamus*, by Clark, W. E. LeG., Beattie, J., Riddoch, G. and Dott, N. M., Edinburgh. Oliver and Boyd, 131–184 (1938) 212 pp.
9. Elterich, T. O. Analysis of syndrome of precocious menstruation. Early puberty (feminine type), premature ripening of skeleton. *Pennsylvania M. J.* **34**: 629–635 (June 1931)
10. Fischer, H. S. Precocious menstruation. *Am. J. Obst. & Gynec.* **39**: 525–527 (March 1940).
11. Ford, F. R., and Guild, H. Precocious puberty following measles encephalomyelitis and epidemic encephalitis, with discussion of relation of intracranial tumours and inflammatory processes to syndrome of macrogenitosomia praecox. *Bull. Johns Hopkins Hosp.* **60**: 192–203 (March 1937)
12. Freedman, H. J. Disturbances of function of the suprarenal glands in children. *Am. J. Dis. Child* **44**: 1285–1292 (Dec. 1932)
13. Gross, R. E. Neoplasms producing endocrine disturbances in childhood. *Am. J. Dis. Child* **59**: 579–628 (March 1940)
14. Hain, A. M. Adrenal Tumours and Pseudohermaphroditism: a hormone study of cases. *J. Path. & Bact.* (1946) in press.
15. Hain, A. M. and Robson, J. M. Comparative assay of oestrone in rat and mouse. *J. Pharmacol. & Exper. Therap.* **57**: 337–346 (Aug. 1936)
16. Halban, J. Tumoren und Geschlechtscharaktere. *Ztschr. f. Konstitslehre* **11**: 294–326 (1925).
17. Harris, R. H. Carcinomatous ovarian teratoma with premature puberty and precocious somatic development. *Surg. Gynec. & Obst.* **41**: 191–193 (Aug. 1925)
18. Harvey, W. G. A case of precocious sexual development. *Irish J. M. Sc.* Fifth Series, 550–551 (Feb. 1923).
19. Hoag, L. A. Malignant hypernephroma in children. *Am. J. Dis. Child.* **25**: 441–454 (June 1923).
20. Kayne, G. G., Babcock, W. W., Beates, H. and Jump, H. D. Cited by Halban (16) (1925) q.v. and probably same case as reported by Jump, H. D., Beates, H. and Babcock, W. W. Precocious development of external genitals due to hypernephroma of adrenal cortex. *Am. J. M. Sc.* **147**: 568–574 (1914).
21. Kepler, E. J., Walters, W. and Dixon, R. K. Menstruation in child aged 19 months as result of tumour of left adrenal cortex: Successful surgical treatment. *Proc. Staff Meet. Mayo Clin.* **13**: 362–366 (June 8, 1938).
22. Knewitz, O. W. Adeno-carcinoma of the ovary in a 5 year old girl. *Illinois M.J.* Chicago **37**: 407 (June 1920), cited by Freedman (12) (1932) q.v.
23. Kraus, E. J. Über Prolanausscheidung bei chronischem Hirndruck. Zugleich ein Beitrag zur Genese der kleincystischen Degeneration der Ovarien. *Klin. Wchnschr.* **11**: 1577–1580 (Sept. 17, 1932).
24. Lenz, J. Vorzeitige Menstruation, Geschlechtsreife und Entwicklung. *Arch. f. Gynäk.*, **99**: 67–144 (1913).
25. Lesser, E. Ein Fall von Hypertrichosis universalis und frühzeitiger Geschlechtsreife *Ztschr. f. klin. med.* **41**: 122–129 (1900).
26. McCune, D. J. Osteitis fibrosa cystica: the case of a 9 year old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism. *Am. J. Dis. Child.* **52**: 743–747 (1936).
27. Novak, E. Granulosa-cell ovarian tumours as a cause of precocious puberty with a report of 3 cases. *Am. J. Obst. & Gynec.* **26**: 505–519, (Oct. 1933).

28. Novak, E. The constitutional type of female precocious puberty with report of 9 cases. *Am. J. Obst. & Gynec.* **47:** 20–42 (Jan. 1944).
29. Palmer, A. Estrogenic hormone in urine and tumour of a patient with granulosa-cell tumour of ovary. *Am. J. Obst. & Gynec.* **37:** 493–494 (March 1939).
30. Reilly, W. A., Lisser, H., and Hinman, F. Pseudo-sexual precocity—the adrenal cortical syndrome in pre-adolescent girls. *Endocrinology* **24:** 91–114 (Jan. 1939).
31. Russell, W. O., and Sachs, E. Pinealoma: A clinico-pathologic study of 7 cases with a review of the literature. *Arch. Path.*, **35;** 869–888 (June, 1943).
32. Talbot, N. B., Butler, A. M., and MacLachlan, E. A. Alpha and beta neutral ketosteroids (androgens): preliminary observations on their normal urinary excretion and clinical usefulness of their assay in differential diagnosis. *New England J. Med.* **223:** 369–373 (1940); cited by Warren (36) (1945) q.v.
33. Venning, E. H. Further studies of the estimation of small amounts of sodium pregnanediol glucuronidate in urine. *J. Biol. Chem.* **126:** 595–602 (Dec. 1938).
34. Walters, W., and Kepler, E. J. Surgical lesions of the adrenal glands. *J.A.M.A.* **111:** 1061–1065 (Sept. 17, 1938).
35. Walters, W., Wilder, R. M., and Kepler, E. J. Suprarenal cortical syndrome with presentation of 10 cases. *Ann. Surg.* **100:** 670–688 (Oct. 1934).
36. Warren, F. L. Estimation of 17-ketosteroids in diagnosis of adrenal cortical tumours. *Cancer Research* **5:** 49–54 (Jan. 1945).
37. Weinberger, L. M. and Grant, F. C. Precocious puberty and tumours of the hypothalamus. Report of case and review of literature, with pathophysiologic explanation of precocious sexual syndrome. *Arch. Int. Med.*, **67:** 762–792 (April 1941).
38. Werner, A. A. *Endocrinology: Clinical Application and Treatment* (2nd Edition). Philadelphia, Lea and Febiger, pp. 118, 417, 782 (1942)
39. Young, H. H. *Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases.* London, Baillière, Tindall and Cox. 649 pp. (1937).

AN EVALUATION OF THE URETHRAL SMEAR AS AN INDEX OF ANDROGENIC DEFICIENCY IN THE MALE

EUGENE J. COHEN

From the Department of Medicine, Cornell University Medical College and the New York Hospital, New York City

IN a communication to this Journal Andrews (1) suggested the use of urethral smears as an index of androgen deficiency in males. He reported that smears of the distal cells of the male urethra showed characteristic staining reactions with the Shorr stain (2) indicating the presence or absence of an androgen deficiency. The urethral cells of normal individuals were said to appear as masses of cuboidal cells with rather pink staining cytoplasm and with very distinct brown nuclei. On the other hand, where an androgen deficiency was present the cytoplasm stained blue and the nuclei red. Where androgen therapy was given to correct a deficiency of this hormone, the staining reaction of the urethral smear was found to change, eventually becoming characteristic of the normal individual. Such findings, if confirmed, would indeed have much clinical diagnostic significance. We have undertaken a study of this technic with results which do not support the observations reported by Andrews.

METHODS

A urethral smear is taken by spreading open the meatus and applying a dry slide to the inner moist surface. The slide is fixed immediately in a solution of equal parts of ether and 95% alcohol and then stained with the Shorr stain. We have found that if more than one to two seconds elapse between the taking of the urethral smear and its fixation, a "dry smear" results in which most cells will take a diffuse orange-red stain. This distortion of the staining reaction by the drying of the smear before fixation can obviously lead to an erroneous interpretation of its cytology.

Shorr (2) has described the use of a mixture of equal parts of glycerin and 95% alcohol for the prevention of drying of the vaginal secretion before fixation in certain cases in which very scant vaginal secretion is present. We have used such a glycerin-alcohol mixture for preparing urethral smears in the present study by the following procedures: 1. A drop of the mixture is spread thinly over the slide and this area applied several times to the inner lips of the meatus. 2. A drop of the mixture is placed in the meatus by means of a glass rod before applying a dry slide to this region. 3. A glass rod moistened with the mixture is introduced about one-fourth of an inch

Received for publication Dec. 12, 1946.

within the meatus, the rod rotated three or four times, and the urethral cells thus obtained are spread on a slide. The smears obtained by these procedures are promptly fixed in the ether-alcohol solution and stained in the usual manner.

Fifteen normal and fifteen hypogonadal males were studied in this series.

RESULTS

No significant differences were observed in the staining reactions of the urethral smears of normal and hypogonadal subjects. In both groups a mixed cytological picture was obtained, the smears consisting of typical cornified squamous cells and non-cornified cells of varying shapes and sizes. In the smear obtained by the direct application of the slide to the meatus according to the method of Andrews and fixed promptly, the non-cornified cells occupied the central area of the smear while the cornified cells were usually distributed in the periphery. This suggested that the non-cornified cells had their origin in the moist urethral mucosa, while the cornified cells were largely derived from the mucocutaneous junction of the glans and mucosa. This was shown to be the case by the use of the glass rod technic in which the rod was moistened with the glycerin-alcohol mixture and applied directly to the moist surface of the urethra. Smears thus obtained were virtually devoid of cornified cells.

Smears taken by any of the technics employed in this study consisted predominantly of non-cornified cells of a wide variety of shapes and sizes and with a cytoplasm which stained a bluish green. They included small cuboidal cells with large nuclei and small amounts of cytoplasm, somewhat larger round or oval cells with large nuclei containing chromatin granules, larger squamous cells with large vesiculated nuclei, and thin wafer-like squamous cells of large size containing small pyknotic nuclei. Except for the small cuboidal cells, and rarely, a few columnar cells, these non-cornified cells were counterparts of cells observed in the vaginal secretion. The cornified cells consisted of two types, a large flat squamous cell with a small pyknotic nucleus, and nondescript irregular cells frequently devoid of nuclei. The percentage of the various non-cornified cell types changed from day to day, and even on the same day in the same subject. These variations in cell types and the absence of detectable significant differences in the urethral smears of normal and hypogonadal males invalidate the diagnostic significance of the urethral smear as a measure of androgenic hormone formation.

In addition to the above study, two normal males were given 5 mg. of estrone sulfate (Premarin) daily for two weeks by mouth; following this, daily injections of 10,000 R.U. of estradiol benzoate were given to one subject for two weeks and to the other subject for three weeks without there being any significant changes in the urethral smear. In the latter sub-

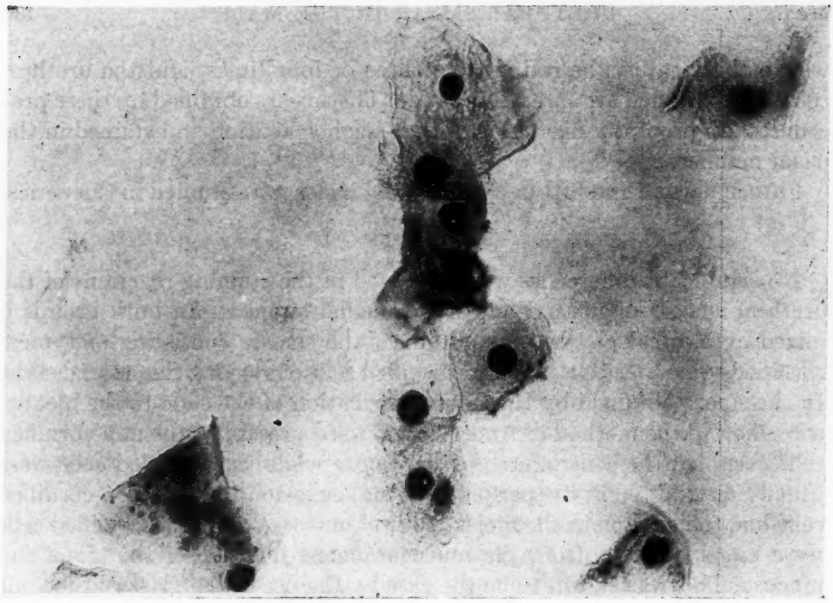

FIG. 1A. Urethral smear of a normal male C.E., age 34; urinary 17-ketosteroid excretion, 14.3 mg./24 hrs. ×600.

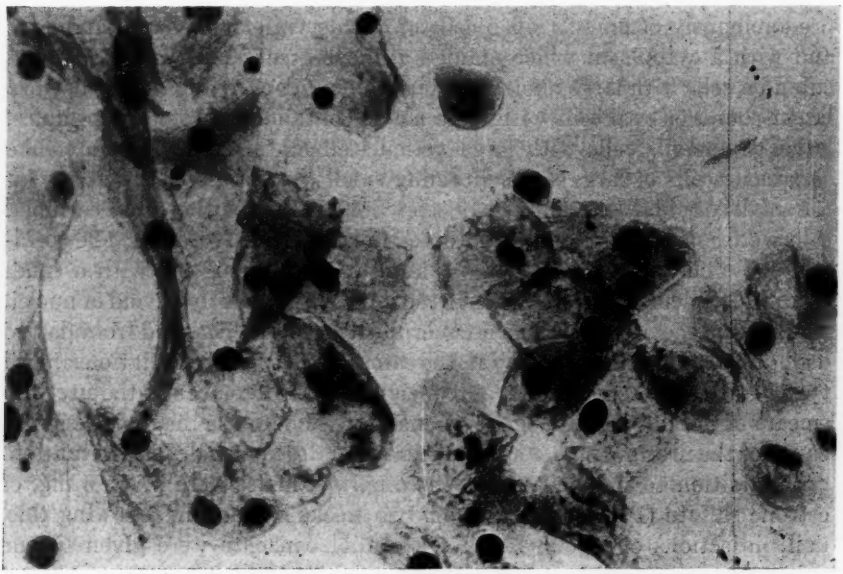

FIG. 1B. Urethral smear of the same subject C.E. after receiving 5 mg. of estrone sulfate (Premarin) daily for two weeks by mouth and then daily injections of 10,000 R.U. of α-estradiol benzoate for three weeks. ×600.

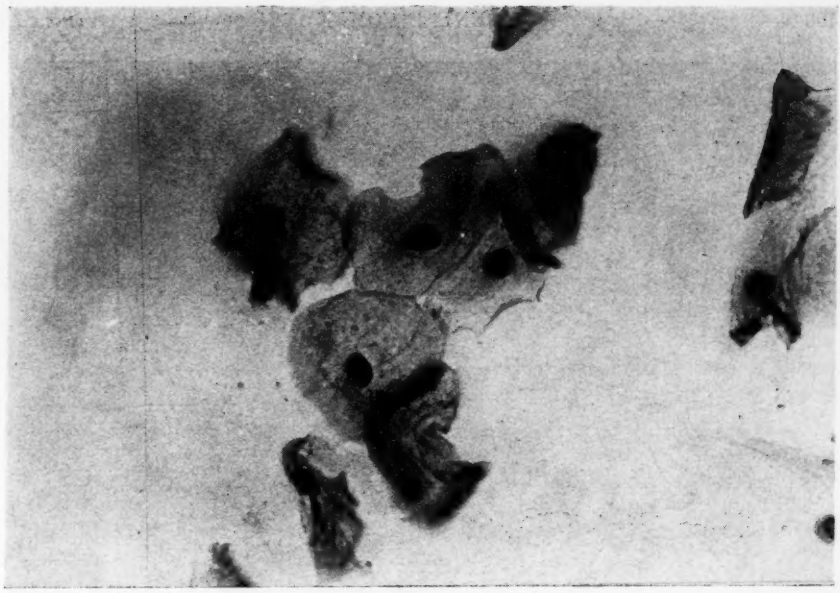

FIG. 2A. Urethral smear of a hypogonadal male W.S., age 35; urinary 17-ketosteroid excretion, 7.0 mg./24 hrs. (values for normal males in this laboratory, 9–16 mg./24 hrs.). ×600.

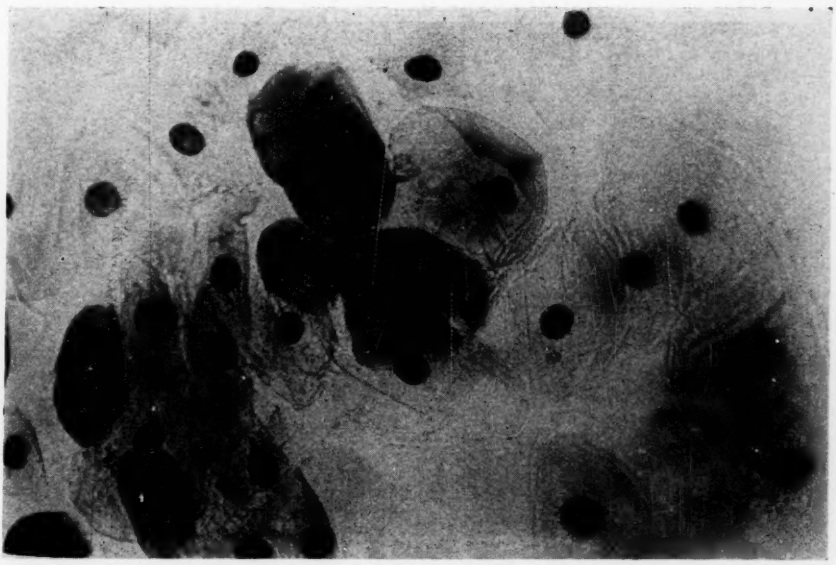

FIG. 2B. Urethral smear of the same subject W.S. after the oral administration of 20–30 mg. of methyl testosterone daily for 2½ months resulting in an increase in size of the penis, increase in libido, potency and hair growth, all indicating adequate replacement therapy. ×600.

FIG. 3. Urethral smear of a hypogonadal male E.K., age 47; urinary 17-ketosteroid excretion, 3.1 mg./24 hrs. ×600.

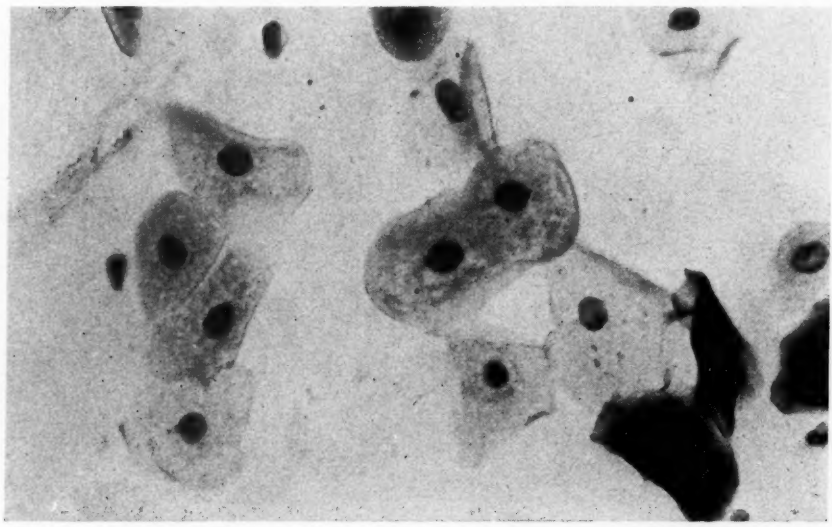

FIG. 4. Urethral smear of a hypogonadal male W.M., age 42; urinary 17-ketosteroid excretion, 2.1 mg./24 hrs. ×600.

ject, semen analyses and measurements of urinary 17-ketosteroids were carried out. The amount of estrogen administered was found sufficient to produce an oligospermia, a marked change in the morphology of the sperms, and a marked reduction in the volume of the ejaculate; the 17-ketosteroids were lowered from 14.3 mg. to 8.1 mg./24 hrs. at the end of the fourth week of estrogen therapy.

CONCLUSIONS

1. No significant differences are observed in the cytological picture of the urethral smear of normal and hypogonadal males.

2. Errors in interpretation of urethral smears may arise from drying of the smear prior to fixation. Procedures are described by which such drying can be prevented.

ACKNOWLEDGMENT

Acknowledgment is made to Dr. Erwin Schwenk of the Schering Corporation, Bloomfield, N. J., for methyl testosterone (Oreton-M) and for α-estradiol benzoate (Progynon-B); and to Ayerst, McKenna & Harrison, Ltd., New York, N. Y. for the estrone sulfate (Premarin).

REFERENCES

1. Andrews, D. L. A simple test for hormone deficiency in the male. *J. Clin. Endocrinol.* **6:** 516–519 (July, 1946).
2. Shorr, Ephraim. An evaluation of the clinical applications of the vaginal smear method. *J. Mt. Sinai Hosp.* **12:** 667–688 (May–June, 1945).

EFFECTS OF STEROID HORMONES UPON THE DEVELOPMENTAL SEPARATION OF THE PREPUCE FROM THE GLANS PENIS[a]

L. J. WELLS AND CURTIS J. LUND

Department of Anatomy and Department of Obstetrics and Gynecology, University of Minnesota, Minneapolis

IT has been reported that by the tenth day after birth the normal separation of the prepuce from the glans penis has become complete enough "to allow mechanical retraction without danger of a tear."[b] However there are still those infants who are said to present clinical indications for circumcision. From experimental studies in animals it would seem that in these infants such therapeutical agents as androgen might be as effective as cutting.

In rodents, a developmental separation similar to the normal one of puberty may be induced experimentally by subjecting immature ground squirrels to subcutaneous injections of androgen (16). Similar observations in the rat and the mouse have been made (9, 14). It has also been found that in the rat the local application of androgen to the penis is followed by considerable growth of this organ (18).

The first objective of the present study was to determine whether androgen applied to the prepuce of rodents would cause a separation of the foreskin without causing an extensive growth of the penis. The second objective was to determine whether steroid hormones given in this manner to infants would accomplish the same purpose as circumcision without causing undesirable "side effects."

Received for publication December 5, 1946.

[a] Aided by a grant from Ciba Pharmaceutical Products, Incorporated. The steroid hormones, Perandren and Di-ovocylin, were supplied by this firm through the courtesy of Ernst Oppenheimer, M.D.

[b] In the normal development and separation of the human prepuce, the embryonic primordium appears at about the 20-mm. stage (8). The primordium is a fold which consists of an outer sheet of ectoderm and an inner mass of mesoderm. As this fold enlarges it "flows" over the dorsum of the naked glans and eventually its right and left portions extend to the ventral aspect where they unite to produce the frenulum preputii. The epithelium of the prepuce fuses with that of the glans to form a solid layer, the so-called glandar lamella or balano-preputial lamella. Normal separation involves keratinization of this lamella and it begins about the sixth lunar month (2). Early manifestations are a desquamation near the tip of the glans and a formation of epithelial pearls at the site of the future collum glandis. Thereafter the keratinization proceeds from these points toward the center of the lamella. At birth the normal separation of the prepuce is still incomplete.

ANIMALS

For the experiments in rodents the immature male ground squirrel (Citellus tridecemlineatus) was chosen. In this species the glans cannot be exposed manually until about the seventh month of postnatal life (December). The experiments were performed during October and early November.

A solution of testosterone propionate in propylene glycol was dropped on the prepuce by means of a blunted hypodermic needle (gauge 20). The concentration of the solution was such that each drop contained 0.2 mg. (20 mg. per cc.). Beginning on October 8, each of four animals was given one drop per day for a period of 27 days.

It was observed that on the fourth day of treatment there was considerable hypertrophy of the prepuce of each animal. On the seventh day the prepuce of one animal was large enough and free enough so that slight manual retraction exposed about half of the glans. Eventually the foreskin of each animal could be easily and completely retracted, as in a normal adult (days 16, 19, 23, and 25).

TABLE 1. EFFECTS OF ANDROGEN UPON THE REPRODUCTIVE ORGANS OF GROUND SQUIRRELS*

Animals	Body wt., Gm.	Weight of organs, mg.		
		Penis	Seminal vesicles	Prostate
Control	190	109.1	6.5	3.0
Experimental	220	187.6	22.7	9.2
Experimental	230	199.0	17.1	9.2

* For additional explanation, see text.

On November 9, thirty-two days after the initial treatment and five days after the last, two of the experimental animals and one untreated control were autopsied. The data obtained at autopsy (Table 1) indicate that the androgen had caused growth of the penis, seminal vesicles and prostate. Yet all of these organs were much smaller than those of normal adult males. Stated differently, the weight of the organs of the experimental animals suggests that only a small amount of the androgen had entered the blood stream. As additional support for this view, data from an earlier paper may be cited: in 38 normal immature males the average weight of the seminal vesicles was 11.6 mg., while in 3 immature males receiving subcutaneous injections of testosterone propionate the average weight was 590.8 mg. (0.5 mg. of hormone per day for periods of 18 to 22 days) (17).

INFANTS

During the several periods of study, all normal "mature" males born at a local hospital were used. These infants remained in the hospital throughout the period of treatment.

The procedure was as follows. On the day of birth the prepuce was carefully retracted manually so that not a single adhesion would be broken. The greatest transverse diameter of the glans thus exposed was measured by means of calipers which were graduated to tenths of a millimeter. Usually treatment was begun on the day of birth and continued daily for various periods of time. The nurses were instructed not to retract the prepuce of any baby in the hospital.

It did not seem worth while to obtain data on the length and diameter of the penis since at any time the dimensions would depend upon the amount of blood in this erectile organ. Also, since spontaneous erections were observed in several of the controls at the time when the diaper was being changed, it was decided not to keep a record of the number of erections per baby.

The usual method of treatment was for one of the authors (L.J.W.) 1) to wrap the prepuce loosely around the mouth of a hypodermic syringe (0.25 cc.), 2) to press the plunger until 0.05 cc. of the solution of hormone had entered the space between prepuce and glans (frequently it also entered the urethra), 3) to remove the syringe and then use two fingers and thumb for spreading the solution over the entire prepuce and 4) to allow about a minute for partial evaporation of the solvent before permitting the prepuce to touch the diaper. When the treatments were made twice daily, they were spaced about 12 hours apart.

A second method was used only in the case of nine infants (Group D, Table 3). Nurses were instructed to use a calibrated medicine dropper which delivered 44 drops per cc. They were also told to let one drop fall upon the prepuce at the time of each feeding. In order to minimize the chances of error, they were asked to treat all male infants in the hospital until further notice.

Usually on the day after the last application, the prepuce of each infant was retracted by one of the authors (C.L.) and the glans penis was measured by the other (L.J.W.). With respect to procedure, the prepuce was retracted manually as far as possible without tearing adhesions (if present) and the greatest transverse diameter of the portion of glans in view was measured and recorded. Then the tip of a closed hemostat was placed in the space between prepuce and glans and the foreskin was gently stretched by opening the jaws of the instrument. If, because of adhesions, it was still impossible to complete the retraction manually without causing trauma, such adhesions were broken by means of a probe. Finally, as soon as the

retraction had been completed, the glans was returned to its sheath.

Regarding the controls, it may be noted that in all except four of them (71%) a complete retraction was accomplished without cutting (Table 2). That this was possible in certain controls is evidence against the notion that a firm union of glans and prepuce at birth is a reliable indication for circumcision (Infants 2, 3, 7, 10, 11 and 12). At the time of retraction by means of instruments, exactly half of the controls showed adhesions that were quite firm. When bleeding occurred after adhesions had been broken, there

TABLE 2. OBSERVATIONS IN INFANTS (CONTROL SERIES)

Infants	Blank applications (days)[a]	Age at retraction (days)	Body weight (gm.)		Glans free of adhesions (diameter, mm.)		Retraction by means of hemostat and probe	Adhesions[b]	Bleeding after breaking adhesions
			At birth	At retraction	At birth	At retraction			
1	20 P	32	2837	3574	3.5	5.0	Complete	++	0
2	0	28	3603	4057	0.0	3.8	Complete	++	0
3	0	24	2894	2997	0.0	4.0	Complete	+	0
4	0	18	3348	3433	5.7	7.5	Complete	+++	+
5	0	18	3660	3774	0.0	0.0	Partial	+++	+
6	0	17	3221	3206	2.9	4.1	Complete	++	+
7	0	17	3632	3916	0.0	1.8	Complete	++	+
8	14 P	15	3376	3376	0.0	0.0	Contraindicated	+++	+
9	0	15	2497	2951	1.5	3.6	Contraindicated	+++	+
10	13 P	14	3859	3859	0.0	1.3	Complete	+++	+
11	12 S	13	3462	3462	0.0	4.0	Complete	+++	+
12	0	12	3860	3774	0.0	3.6	Complete	++	0
13	0	12	3539	3617	3.0	3.4	Complete	++	0
14	0	8	2922	2951	0.0	0.0	Contraindicated	+++	+

[a] Propylene glycol (P) or sesame oil (S).

[b] +++, quite firm; ++, moderately firm; +, slightly firm.

was generally a single drop of blood which came from the region of the frenulum. In Infant 5, the bleeding began as soon as the jaws of the hemostat had been spread to 3.7 mm. and the retraction was not completed because the prepuce was so thin and unyielding. In Infants 8 and 14, a spread of 3.5 mm. caused bleeding, while in Infant 9, a spread of 6.0 mm. caused it.

In the experimental series (Table 3), complete retraction was possible in 22 of the 27 cases (81%). Five of the infants showed no adhesions. Of those having adhesions, Infant 36 was the only one in whom they were quite firm. It would seem, then, that one effect of the hormones was a softening of the adhesions. In most cases as soon as the hemostat had been spread and the prepuce had been pulled back as far as possible without tearing, a ring of smegma was observed at the junction of prepuce and glans. Doubt-

TABLE 3. OBSERVATIONS IN INFANTS (EXPERIMENTAL SERIES)

Groups	Infants	Application of hormones (days)	Age at retraction (days)	Body weight (gm.)		Glans free of adhesions (diameter, mm.)		Retraction by means of hemostat and probe	Adhesions[a]	Bleeding after breaking adhesions
				At birth	At retraction	At birth	At retraction			
				Androgen in propylene glycol, one application per day (1.0 mg. daily)						
A	15	25	26	3036	3291	0.0	7.3	Complete	0	0
	16	23	27	3447	4001	0.0	2.5	Complete	+	+
	17	20	21	3774	3887	2.4	12.6	Complete	0	0
	18	20	25	2781	3036	4.1	7.2	Complete	+	0
				Androgen in propylene glycol, two applications per day (2.0 mg. daily)						
B	19	17	23	3348	3603	0.0	3.4	Almost complete	0	0
	20	17	22	3802	4129	0.0	12.6	Complete	+	0
	21	16	17	3830	3774	0.0	5.6	Complete	+	+
	22	15	16	3334	3603	0.0	4.7	Complete	++	+
	23	14	15	3518	3660	2.0	6.5	Almost complete	+	0
	24	13	14	4731	4540	4.0	7.0	Complete	+	0
				Androgen in sesame oil, two applications per day (2.5 mg. daily)						
C	25	14	15	2873	3235	5.7	9.0	Complete	+	0
	26	13	14	3646	3745	2.7	13.5	Complete	0	0
	27	13	14	3873	4001	0.0	9.2	Complete	+	0
	28	12	13	3901	3916	2.7	5.7	Complete	+	+
	29	12	13	3462	3405	0.0	9.0	Complete	0	0
	30	10	11	3008	3036	0.0	3.0	Complete	+	+
				Androgen in propylene glycol, six applications (drops) per day (3.0 mg. daily)						
D	31	13	24	3547	3916	0.0	5.6	Partial	++	+
	32	13	21	3121	3178	0.0	7.1	Complete	+	0
	33	12	28	3235	3405	0.0	6.0	Complete	++	+
	34	12	23	3689	3887	0.0	2.3	Partial	++	+
	35	12	22	2922	3234	0.0	4.8	Complete	+	0
	36	12	22	3405	3376	0.0	3.5	Contraindicated	+++	
	37	12	21	3192	3674	0.0	5.9	Complete	+	+
	38	12	17	3121	3163	0.0	4.0	Complete	+	0
	39	8	30	3348	3745	2.3	6.2	Complete	+	+
				Estrogen in sesame oil, two applications per day (0.5 mg. daily)						
E	40	8	9	3972	3603	2.3	5.8	Complete	+	+
	41	6	7	3405	3178	2.3	2.5	Complete	+	0

a. +++, quite firm; ++, moderately firm; +, slightly firm.

less this material must have originated from the breakdown (cornification) of the distal portion of the glandar lamella.[b]

Retraction was easiest in the infants of Group A. While it seemed that

the glans was somewhat larger than that of controls, the prepuce was so large and pliable that there was little difficulty in completing the retraction. In Infants 15 and 17, the retraction was readily completed without instruments. These observations suggest that the application of 1.0 mg. once daily for three weeks is more effective than the application of 1.25 mg. twice daily for two weeks (Groups A and C).

In Groups B and C, it seemed that the glans had grown as rapidly as the prepuce. From the standpoint of retraction, this growth of the glans was undesirable. In fact, in Infants 19 and 23, it was decided not to try to complete the retraction because the glans was disproportionately large in comparison with the prepuce.

Yet the growth of the penis had not been undesirably rapid. Infants 18 and 20 were observed again on the 36th and 39th day after birth, respectively, and it was noted that the penis was not undesirably large.

From memory and general impression, the frequency of erections in the experimental series was about the same as that in the control series. Infant 22, however, was exceptional in that his penis became erected nearly every time an application was made.

In Group D the treatments were begun at birth but were discontinued several days before the retraction. The data would seem to indicate that applying 3.0 mg. per day for two weeks was less effective than applying 1.0 mg. per day for three weeks (Groups D and A). However in Group D it is possible that the effects of treatment had disappeared in part during the interval of non-treatment. Certainly at the time of retraction the glans was not disproportionately large.

Estrogen also caused a loosening of adhesions but failed to cause any detectable growth of the penis (Group E). Only one control showed adhesions that were slightly firm and this control was 26 days of age (Infant 3). Presumably the estrogen acted by causing growth and cornification of the balano-preputial epithelium. In this connection it may be mentioned that when estrogen acts in this manner upon the vaginal epithelium of immature rats it causes the developmental opening of the vagina (1).

DISCUSSION

The question arises as to why the androgen induced a complete separation of the prepuce in only twenty per cent of the infants of Groups A to D (Infants 15, 17, 19, 26 and 29). While the data are not adequate to permit a definite answer, they suggest that the main factor was the relatively short periods of treatment. Certainly in the seven infants who received treatment for periods of 16 to 25 days there was an absence of adhesions in a much higher percentage of cases (43%). It may be recalled that in the individual

experimental animals the disappearance of adhesions occurred on days 16, 19, 23 and 25.

The data also suggest that applying androgen in sesame oil was equally as effective as applying it in propylene glycol. In appraising the relative effectiveness of these methods, two important variables must be kept in mind, namely, the number of applications and the quantity of hormone.

Absence of marked growth of the penis suggests that a relatively small quantity of the androgen had entered the circulation. Doubtless only a small quantity of the estrogen had entered it. Consequently it is reasonable to suppose that these steroid hormones had not caused any undesirable effects upon skeleton and internal reproductive organs.[c]

It is not the purpose of this paper to discuss the controversial problem of circumcision. The physician who more or less routinely practices this procedure would not find the use of androgen especially helpful. On the other hand we do not subscribe to such routine and our opinion is shared by many clinicians. There are two distinct purposes of circumcision. One is to permit complete retraction of the prepuce and the other is to remove part of an excessively long prepuce. We have no evidence that androgen affects the length of the prepuce but it does reduce the adhesions which commonly hinder normal retraction. It was possible to retract the foreskins of all treated babies in groups A, B and C satisfactorily, yet it was not possible in 29 per cent of a control group of comparable size.

Two difficulties arise when this method is applied clinically. The first of these is time. The data suggest that treatment for 20 to 25 days produced better results than did shorter periods of treatment. Rarely do newborn infants remain in the hospital for more than 10–15 days at present. While it might be possible to continue such treatments in the home, our data suggest that skill and care in the topical application are of considerable importance.[d] The second difficulty, of minor importance, was the tendency of

---

[c] Any notion that our treatment of these infants might have led to premature development of the skeleton deserves little more than passing attention. The fetus is normally exposed to those estrogenic and androgenic substances which are in the fluids of pregnancy (4, 6). Also the quantity of hormone and the duration of treatment were negligible in comparison with those which have been reported to accelerate the development of the skeleton (10) (cf. effects of gonadotropin) (3). Nor is there reason to suspect that our treatments caused permanent effects upon spermatogenesis. While steroid hormones may inhibit spermatogenesis by acting upon the anterior hypophysis (12), the effects are reported to be more or less temporary (7, 11, 19). In 1942 Moore and Morgan concluded that "The effects of androgens upon the testis remain an open question" (13). Subsequently it has been reported that in hypophysectomized animals the injection of androgen will maintain spermatogenesis (5), will restore spermatogenesis (15) and will even induce the precocious formation of spermatozoa (17).

[d] It is likely that androgen in the form of an ointment could be satisfactorily applied

the glans to enlarge. While this was of no clinical significance it did tend to offset some of the advantages obtained by the reduction of adhesions.

Finally, the direct application of androgen is apparently of limited value in those very infants who present clinical indications for circumcision.

SUMMARY

The topical application of testosterone propionate to the prepuce of immature ground squirrels induced a developmental separation of the prepuce from the glans penis. This treatment caused only slight growth of such accessory reproductive organs as the penis, the seminal vesicles and the prostate.

Similar treatment of infants caused a complete separation of the prepuce in 5 of the 25 cases (20%). In most of the other cases this treatment led to a softening of those adhesions which commonly hinder the normal retraction of the foreskin. Likewise the topical application of estradiol dipropionate was followed by a loosening of such adhesions. These steroid hormones did not cause any undesirable "side effects."

REFERENCES

1. Allen, E. and Doisy, E. A. The induction of a sexually mature condition in immature females by injection of the ovarian follicular hormone. *Am. J. Physiol.* **69**: 577–588 (Aug. 1924).
2. Deibert, G. A. The separation of the prepuce in the human penis. *Anat. Rec.* **57**: 387–399 (Nov. 25, 1933).
3. Dorff, G. B. Chorionic gonadotropic effects on height and osseous development in sexually under-developed young boys. *Endocrinology* **27**: 403–410 (Sept. 1940).
4. Dorfman, R. I., and Van Wagenen, G. The sex hormone excretion of adult female and pregnant monkeys. *Surg., Gynec., & Obst.* **73**: 545–548 (Oct. 1941).
5. Dvoskin, S. Local maintenance of spermatogenesis in hypophysectomized rats with low dosages of testosterone and intratesticular pellets. *Proc. Soc. Exper. Biol. & Med.* **54**: 111–113 (Oct. 1943).
6. Fraenkel, L. and Papanicolaou, G. N. Growth, desquamation and involution of the vaginal epithelium of fetuses and children, with a consideration of the related hormonal factors. *Am. J. Anat.* **62**: 427–451 (May 1938).
7. Greene, R. R. and Burrill, M. W. The recovery of testes after androgen induced inhibition. *Endocrinology* **26**: 516–518 (March 1940).
8. Hunter, R. H. Notes on the development of the prepuce. *J. Anat.* **70**: 68–75 (Oct. 1935).
9. Lyons, W. R., Berlin, I., and Friedlander, S. Cornification of the balano-preputial epithelium in normal rats and in castrated rats treated with testosterone propionate. *Endocrinology* **31**: 659–663 (Dec. 1942).

---

to the prepuce of an infant by the parents. We did not use this form of treatment because testosterone propionate is much more soluble in oil than in an ointment base. Incidentally, applying androgen in propylene glycol is less satisfactory than applying it in oil since micturition would remove the former solvent more readily than the latter.

10. McCullagh, E. P. and McGurl, F. J. The effects of testosterone propionate on epiphyseal closure, sodium and chloride balance and on sperm counts. *Endocrinology* **26**: 377–384 (March, 1940).
11. Matthews, C. S., Schwabe, E. L., and Emery, F. E. Studies on recovery of the reproductive system of the male rat from regressive changes induced by stilbestrol. *Endocrinology* **30**: 89–92 (Jan. 1942).
12. Moore, C. R. and Price, D. Gonad hormone functions and the reciprocal influence between gonads and hypophysis with its bearing on the problem of sex-hormone antagonism. *Am. J. Anat.* **50**: 13–71 (March, 1932).
13. Moore, C. R., and Morgan, C. F. Responses of the testis to androgenic treatments. *Endocrinology* **30**: 990–999 (June, 1942).
14. Raynaud, A. et Lacassagne, A. Influence de l'hormone male et de l'hormone femelle sur la structure histologique du pénis de la souris. *Compt. rend. Soc. de Biol.* **126**: 868–871 (1937).
15. Smith, P. E. Maintenance and restoration of spermatogenesis in hypophysectomized rhesus monkeys by androgen administration. *Yale J. Biol. & Med.* **17**: 281–287 (Oct. 1944).
16. Wells, L. J. (1932, unpublished observations).
17. Wells, L. J. The response of the testis to androgens following hypophysectomy. *Anat. Rec.* **82**: 565–585 (April 25, 1942).
18. Wigodsky, H. S. and Greene, R. R. The effect of testosterone, estrone and estradiol applied locally to the penis of the rat. *Endocrinology* **26**: 1078–1080 (June, 1940).
19. Wilson, J. G., and Wilson, H. C. Reproductive capacity in adult male rats treated prepuberally with androgenic hormone. *Endocrinology* **33**: 353–360 (Dec. 1943).

EXCRETION OF 17-KETOSTEROIDS IN ANKYLOSING SPONDYLARTHRITIS AND IN RHEUMATOID ARTHRITIS: A PRELIMINARY REPORT

ROLAND A. DAVISON, PETER KOETS, AND WILLIAM C. KUZELL

From the Departments of Medicine, of Obstetrics and Gynecology, and of Pharmacology and Therapeutics, Stanford University School of Medicine, San Francisco, California

BECAUSE of the peculiar sex distribution of various types of arthritis a study of the urinary 17-ketosteroid excretion was made. No study of this type has previously been reported in arthritic patients. It has long been observed clinically that in ankylosing spondylarthritis (Marie-Strümpell type) there is a great preponderance of males over females. "The highest incidence of females recorded has been 10 per cent" (1). In rheumatoid arthritis, there is a less marked but important preponderance in incidence of the disease in females over males. "Females are much more frequently affected (3:1) than males" (3). In studies of follicle-stimulating-hormone excretion in women under 40 years of age with rheumatoid arthritis Sjövall recently concluded that 21 per cent showed ovarian insufficiency (6).

The 17-ketosteroids are a group of compounds which form the metabolic end-products of steroids originating in the adrenal cortex of the female and in both the adrenal cortex and the gonads of the male. Normally, approximately 90 per cent consists of androsterone and its inactive isomer, 3-hydroxy-etiocholanone, the remainder being mostly dehydro-iso-androsterone which is weakly effective as a male sex hormone. The excretion in normal males varies between 8 and 28 milligrams in 24 hours, average, 14 milligrams; in normal females the limits are 5 to 18 milligrams in 24 hours, average, 9 to 10 milligrams (4). The excretion of 17-ketosteroids is lowered in Addison's disease and in hypothyroidism and moderately increased in hirsutism of females, in masculinizing ovarian tumors, and in Cushing's syndrome. It is, in general, greatly increased in hyperplasia and in carcinoma of the adrenal cortex where excretion values can rise to more than 300 milligrams in 24 hours, although exceptions to this have been noted (2).

In our series of 13 cases of ankylosing spondylarthritis all patients were males, and all showed characteristic x-ray changes in the spine; several also showed some changes in the hips. The small joints of the extremities

Received for publication November 14, 1946.

were not affected in these patients. In this group 10 cases were active, 1 questionably active, and 2 inactive as judged by sedimentation rate and physical findings. The average age for the group was 39.4 years, range, 25 to 43 years. The average duration of symptoms was 10.6 years, range, 3 to 26 years. Two patients had received previous x-ray therapy.

In our series of 11 cases of rheumatoid arthritis all patients were females, and the disease was limited principally to the joints of the extremities. In this group the average age was 40.4 years, range, 25 to 52 years. Eight of

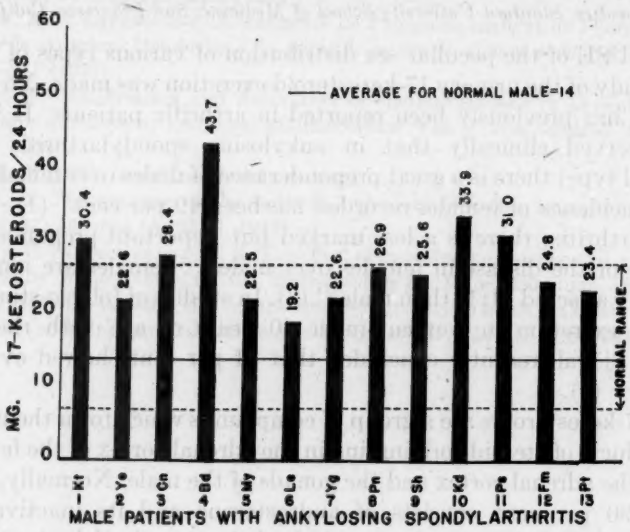

FIG. 1

the 11 patients were receiving chrysotherapy at the time the determinations were made. Ten of the 11 cases were active as judged by sedimentation rate and physical findings, and the average duration of symptoms was 5 years.

METHOD

The method used by us was an adaptation of that of Robbie and Gibson (5). Twenty-four-hour specimens of urine were collected and the volume measured. To 250 cc. of urine were added 25 cc. of concentrated hydrochloric acid and the mixture boiled at a reflux for 7 minutes. After cooling, 60 cc. of carbon tetrachloride were added and the boiling continued on a water bath for 10 minutes. The carbon tetrachloride layer was washed twice with water, twice with 10 per cent sodium hydroxide, and again with water until neutral. After evaporation *in vacuo* the residue was taken up in

10 cc. of absolute alcohol. For the colorimetric measurement, 1 cc. of the extract solution was added to 4 cc. of 95 per cent alcohol, 1 cc. of 2 per cent m-dinitrobenzene in absolute alcohol, and 1 cc. of 15 per cent aqueous potassium hydroxide. The color was read after 90 minutes in a Klett-Summerson colorimeter and compared with a standard prepared from crystalline androsterone. Blanks were run to correct for urinary pigments and for the m-dinitrobenzene color. The 17-ketosteroid excretion was then computed for the total 24-hour volume. Values obtained by this method

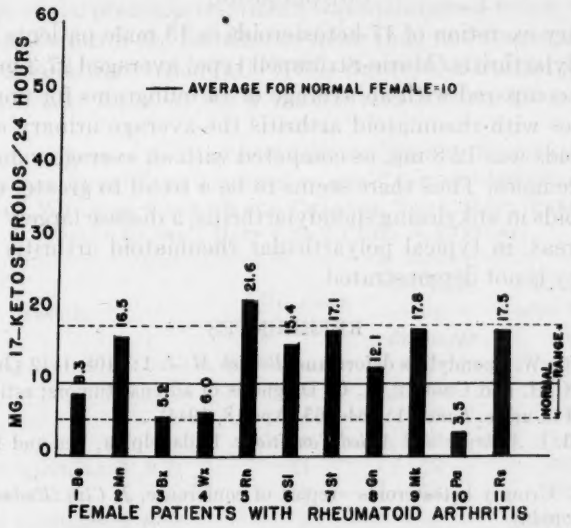

FIG. 2

show excretion of normal adult males varies between 8 and 28 milligrams in 24 hours, average, 14 milligrams; for normal females the limits are 5 to 8 milligrams in 24 hours, average 9 to 10 milligrams.

RESULTS

Figure 1 shows the urinary excretion of 17-ketosteroids in 13 patients with ankylosing spondylarthritis. It is seen that the range is from 19.2 milligrams to 43.7 milligrams in 24 hours, the average for the group, 27.3 mg. The 17-ketosteroid levels in this series group themselves around the upper limit of normal for males.

Figure 2 shows the urinary excretion of 17-ketosteroids in 11 female patients with rheumatoid arthritis. The range in this group is from 3.5 to 21.6 milligrams in 24 hours, average, 12.8 milligrams. The 17-ketosteroid

levels for these patients are scattered through the normal range for females.

A subsequent report will present results of 17-ketosteroid determinations in patients with spondylarthritis during and after treatment with x-ray and in patients with rheumatoid arthritis after chrysotherapy. Similar determinations are being made on patients with gout and on males with rheumatoid arthritis, and attempts will be made to fractionate the ketosteroids when their levels are elevated.

CONCLUSIONS

The urinary excretion of 17-ketosteroids in 13 male patients with ankylosing spondylarthritis (Marie-Strümpell type) averaged 27.3 milligrams in 24 hours as compared with an average of 14 milligrams for normal males. In 11 females with rheumatoid arthritis the average urinary excretion of 17-ketosteroids was 12.8 mg. as compared with an average value of 10 mg. for normal females. Thus there seems to be a trend to greater excretion of 17-ketosteroids in ankylosing spondylarthritis, a disease largely confined to males; whereas, in typical polyarticular rheumatoid arthritis in females, this tendency is not demonstrated.

REFERENCES

1. Buckley, C. W. Spondylitis deformans, *British M. J.* **1**: 1108–1112 (June 27, 1931).
2. Callow, N. H. and Crooke, A. C. Diagnosis of adrenal tumors; estimation of 17-ketosteroid in urine, *Lancet* **1**: 464–465 (April 8, 1944).
3. Comroe, B. I. *Arthritis and Allied Conditions*, Philadelphia, Lea and Febiger, 1944, p. 84.
4. Pincus, G. Urinary ketosteroids—report of conference, *J. Clin. Endocrinol.* **3**: 301–303 (May, 1943).
5. Robbie, W. A. and Gibson, R. B. Rapid clinical determination of urinary 17-ketosteroids, *J. Clin. Endocrinol.* **3**: 200–205 (April, 1943).
6. Sjövall, H. Die Hormonausscheidung bei chronischer Polyarthritis des Weibes, *Acta med. Scandinav.* **117**: 69–89 (1944).

INSULIN REGULATION IN ONE HUNDRED AND TWENTY-SIX DIABETIC CHILDREN*

HERMAN O. MOSENTHAL AND ALBERT P. ROSEN

New York City

THIS report concerns 126 campers during July and August, 1946, at Camp Nyda, the summer camp for diabetic children conducted by the New York Diabetes Association. Each child remained four weeks. The insulin dosage of the precamp treatment was maintained unless the precamp insulin did not control the diabetes or more than morning and evening injections of insulin were scheduled. When the type of insulin was changed, the first shift was made to the 1 part P and 2 parts R—advocated by

TABLE I. TYPES OF INSULIN ADVISED BY CLINICS AND PRIVATE PHYSICIANS FOR THE 126 CHILDREN BEFORE THEY WERE ADMITTED TO THE CAMP AND MODIFICATIONS FOUND ADVANTAGEOUS WHILE AT CAMP (WHEN CHANGES WERE MADE PREFERENCE WAS GIVEN TO THE 1 PART P TO 2 PARTS R MIXTURE)

Insulin	No. cases precamp	No. cases on discharge	No. cases changed after 3 to 4 weeks at camp
P	26	27	1 more
R	14	0	14 less
G	10	10	no change
separate injections: P & R	44	28	16 less
mixtures: P & R	25	54	29 more
separate injections: P & G	4	4	no change
separate injections: R & G	2	2	no change
none	1	1	no change

Colwell (1) as the most nearly universally applicable insulin. Consequently, our discharge types of insulin are weighted in favor of the 1-to-2 mixture.

The standards of diabetes control at Camp Nyda were a sugar free urine and the avoidance of hypoglycemic reactions. These objectives were achieved in nearly all children for most of their stay. The insulin administered at the end of three or four weeks represents the insulin that was finally considered successful in controlling the diabetes under camp conditions of diet and exercise.

Received for publication November 22, 1946.

* In this presentation, protamine zinc insulin is designated by the letter "P," unmodified (regular) and crystalline insulin by "R," globin insulin with zinc by "G." From Camp NYDA conducted by the New York Diabetes Association, Inc.

A summary of the admission and the discharge insulins is given in Table I. Several conclusions from this table are obvious. P or G as the only insulin used was satisfastory in many cases. R alone was a failure in every child receiving this insulin. Separate injections of P and R were not as successful as the mixtures of P and R. Mixtures of P and R proved acceptable in nearly all instances when shifts in the type of insulin were deemed necessary, though in two cases a change to P alone from the P and R mixtures proved to be advantageous. As mentioned above, the mixtures of P and R were immediately resorted to for modification of the kind of insulin, which accounts for the large increase in this type of insulin on discharge. The administration of G and R, and of G and P, gave good results in a few instances. However, the disadvantage of two injections instead of one has to be taken into consideration.

Protamine Zinz Insulin as the Sole Insulin

On admission, 26 children received P, and no other insulin (Table II). In 14, the dose was above 30 units and in 6, above 40. It was considered expedient to shift from P to the 1-to-2 mixture in only 4 instances. This is remarkable because it has been stated over and over again that comparatively few diabetics do well on P alone, and, as stated recently by Palmer, (2) scarcely ever when the dose exceeds 30 units.

An accentuation of the immediately preceding statements is found in Table III which shows that several cases gave evidence of better control of their diabetes with P alone than with combinations of P and R. After several weeks' observation a combination of Tables II and III showed that the level of the P dose had not changed a great deal since 14 children were receiving more than 30 units and 6, more than 40, the identical numbers for the higher doses of P as on admission.

Probably there could have been many more patients successfully managed with P alone, but as stated previously, in making shifts of the type of insulin, the 1-part P to 2-parts R insulin was resorted to in routine fashion.

Unmodified (or Crystalline) Insulin as the Sole Insulin

There were 14 children receiving R as the only insulin according to their precamp record (Table IV). The doses varied from 5 to 70 units by single or multiple injections. When injections were given more often than twice a day (before breakfast and supper) then other types of insulin calling for the administration of one daily dose were substituted. Also, when R alone proved to be unsatisfactory for the control of the diabetes, changes were made. The final result was, as may be noted in Table IV, that R as the sole insulin was rejected in every instance, and other forms of insulin proved to be more suitable for the campers.

TABLE II. 26 CASES RECEIVING P ON ADMISSION TO THE CAMP AND THE SUBSEQUENT MODIFICATION OF INSULIN. IN ONLY 4 CHILDREN WAS IT FOUND NECESSARY TO CHANGE THE TYPE OF INSULIN

P Precamp units	Modification in 3 to 4 weeks
P 15 units	P 20 units
P 20	P 30
P 20	P 28
P 25	P 31
P 25	P 32
P 25	P 30
P 27	P 34
P 28	P 27
P 28	P 29
P 28	1 to 2 mixture* 28 units
P 30	P 28
P 30	P 14
P 32	P 26
P 32	P 14
P 35	P 36
P 39	1 to 2 mixture 45 units
P 40	P 44
P 40	P 34
P 40	P 32
P 40	P 30
P 48	1 to 2 mixture 42 units
P 50	P 42
P 56	P 42
P 56	P 44
P 60	1 to 2 mixture 51 units
P 60	P 44

* 1 to 2 mixture is a mixture containing 1 part P to 2 parts R.

TABLE III. 5 CASES RECEIVING R ONLY OR R AND P AS MIXTURES OR BY SEPARATE INJECTIONS IN WHOM P ALONE PROVED TO BE PREFERABLE

Precamp insulin units	Replaced by P units
R 5 units	P 10 units
R 20 P 60	P 32
R 15 P 45	P 54
R 10 P 30	P 19
R 20 P 40	P 32

TABLE IV. CASES RECEIVING R ONLY ON ADMISSION. IT WAS FOUND ADVISABLE TO CHANGE THE TYPE OF INSULIN IN EACH OF THESE 14 CHILDREN

Total R units precamp	Replaced at camp by	
R 5 units	P 10 units	
R 15	1 to 2 mixture*	18 units
R 15	1 to 2 mixture	15 units
R 20	1 to 2 mixture	24 units
R 26	1 to 2 mixture	24 units
R 27	1 to 2 mixture	18 units
R 35	R 15 P 10 mixture	25 units
R 42	1 to 2 mixture	30 units
R 42	1 to 2 mixture	30 units
R 55	1 to 2 mixture	42 units
R 60	1 to 2 mixture	42 units
R 60	1 to 2 mixture	52 units
R 65	1 to 2 mixture	42 units
R 70	1 to 2 mixture	48 units

* 1 to 2 mixture is a mixture containing 1 part P to 2 parts R.

TABLE V. 16 CASES RECEIVING G ON ADMISSION TO THE CAMP. IN NOT A SINGLE INSTANCE WAS IT FOUND NECESSARY TO CHANGE THE TYPE OF INSULIN

Total G units precamp	Modification in 3 to 4 weeks
G 12 units	G 12 units
G 13	G 32
G 20	G 5
G 30	G 26
G 40	G 36
G 40	G 37
G 50	G 40
G 52	G 46
G 60	G 45
G 60	G 56
G 10 P 40 separate injections	G 12 P 30 separate injections
G 28 P 16 separate injections	G 26 P 18 separate injections
G 36 P 20 separate injections	G 14 P 36 separate injections
G 36 P 54 separate injections	G 20 P 30 separate injections
G 20 R 10 separate injections	G 30 R 9 separate injections
G 34 R 14 separate injections	G 35 R 16 separate injections

Globin Insulin with Zinc

16 cases receiving G on admission (Table V) were continued on the same insulin throughout their stay at camp. The control of the diabetes with G was so satisfastory that we felt it would be worth a more extended trial when other insulins proved inadequate. However, we had committed ourselves to give 1 part P to 2 parts R mixture, and did not deem it wise to switch policies during the two-month period. The more extensive use of G may be taken up in a subsequent session of the Camp. The diet regime with snacks between breakfast and lunch, between lunch and dinner, and at bedtime, besides the three regular meals, is probably a system of feeding particularly adapted to the use of G, and for that matter to the requirements of the 1 part P, 2 parts R mixture, which has an effect a good deal like G.

Combinations of P and R

P and R in combination are administered by three methods: by separate injections, by set mixtures in which the P and R are mixed in a stock vial, and by mixing the P and R in the syringe just before injection which may be given the name "adjustable mixture."

R and P by Separate Injections

There were 44 children, more than a third, on such a schedule, on admission to the camp. This indicates the popularity of using insulin in this way. The amount of insulin given varied enormously. The smallest dose was R 7–P 6, the largest, R 46–P 70. Under camp conditions, this mode of administering insulin was not very successful, as can be gathered from the fact that out of 44 diabetics, this type of insulin therapy was discontinued in 16 (Table I).

Set Insulin Mixtures

Precamp procedures included only 4 of these, two on a mixture of 1 part P to 2 parts R, and two on 7 parts P to 10 parts R. These four cases continued on the same mixture throughout their stay at camp. When other forms of insulin proved unsatisfactory for any reason, transfer was made to a mixture of 1 part P to 2 parts R. This is the proportion advocated by Colwell (1) as the most universally applicable combination of P and R, so that there were 29 children receiving this type of insulin after 3 to 4 weeks' stay at camp (Table VI).

Adjustable Mixtures of P and R

These mixtures, made in one syringe, were used by 21 children on admission to the camp. It may be the mechanical difficulty of measuring two

insulins in one syringe that accounts for this comparatively small number. In our experience, the combination of the two insulins in one syringe was a much more satisfastory method of dispensing insulin than when P and R were given by separate injections. A total of 11 cases receiving separate injections on admission to the camp were benefited by changing over to adjustable mixtures. In all, there were 25 cases receiving adjustable mixtures after 3 to 4 weeks' sojourn at Camp Nyda. Of these, the highest total units was 74, the lowest 18.

TABLE VI. CASES ON SET INSULIN MIXTURES AFTER BEING AT CAMP AND THE TYPE OF INSULIN REPLACED

No. of cases	
4	set insulin mixtures on admission
12	replacing R alone
4	replacing P alone
5	replacing adjustable mixtures
4	replacing separate injections of P and R
29	Total on set mixtures after 3 to 4 weeks at camp

The proportion of P to R in these adjustable mixtures is of interest, since it has often been stated that the amount of P cannot exceed that of R, and prove to be of value. However, in many instances, an excess of P over R proved valuable both under home and camp conditions. (See Table VII.)

TABLE VII. CASES RECEIVING ADJUSTABLE MIXTURES IN WHICH P EXCEEDED R EITHER ON ADMISSION OR AFTER STAY AT CAMP. THIS BY SOME HAS BEEN CONSIDERED A USELESS PROCEDURE, BUT IT APPARENTLY HAS A WIDE APPLICATION. IN NONE OF THE INSTANCES WAS THE DOSE OF INSULIN SO SMALL THAT THE PROPORTION OF P TO R WAS A MATTER OF INDIFFERENCE

Units of P and R mixed in syringe	Total units	Units excess P over R
P 24 R 14	38 units	10 units
P 25 R 10	35	15
P 28 R 18	46	10
P 30 R 10	40	20
P 31 R 10	41	21
P 32 R 29	61	3
P 32 R 20	52	12
P 42 R 15	57	27
P 45 R 15	60	30
P 46 R 20	66	26
P 80 R 24	104	56

SUMMARY AND CONCLUSIONS

The insulin regulation of 126 diabetic children was studied at Camp Nyda during July and August, 1946.

Of the three types of insulin, R, P, and G, when given as the sole insulin, only P and G were satisfactory; in many instances R was a distinct failure. The large doses of P alone, applicable in some instances, are noteworthy; on discharge from the camp 14 children were receiving more than 30 units of P only, and 6 were receiving more than 40 units.

P and R by separate injections had to be replaced by other forms of insulin in many cases. Besides the disadvantage of a double injection, this form of insulin therapy proved less satisfactory than the insulin mixtures made in one syringe.

Insulin mixtures of P and R prepared in one syringe proved effective. Where insulin changes were believed advisable, the routine switch was made to a mixture of 1 part P to 2 parts R advocated by Colwell as the most generally applicable insulin. However, we believe that G would have yielded equally good results. Although the idea that P should not exceed the amount of R in one-syringe mixtures is prevalent, it was shown that on an empirical basis, P was often greater in amount than R for optimal results.

REFERENCES

1. Colwell, A. R. Nature and Time Action of Modifications of Protamine Zinc Insulin, *Arch. Int. Med.* **74**: 331–345 (November, 1944).
2. Palmer, L. J. Insulin in the Treatment of Diabetes Mellitus, *J.A.M.A.* **132**: 502–507 (November 2, 1946).

THYROTOXICOSIS COMPLICATED BY SEVERE IODISM: PREPARATION FOR SURGERY WITH PROPYL-THIOURACIL

EDWARD A. NEWMAN AND PHILIP H. ROSS

From the Medical Service of Dr. William Brams, Michael Reese Hospital, Chicago, Illinois

AS commonly used in the preoperative management of thyrotoxicosis, Lugol's solution is generally considered to have no harmful potentialities. Few instances of severe toxic reactions to this drug are reported in the literature. With the exception of two cases in a series reported by Barker and Wood (3) in 1940, all the reported episodes were mild to moderate in degree. As further evidence that Lugol's solution even in small doses may, on occasion, be a dangerously toxic drug, a case of almost fatal poisoning is here presented.

Case Report: H.B., a negress, age 22, was admitted to the medical service on May 4, 1946, with the classical complaints of hyperthyroidism. Her symptoms were nervousness, insomnia, marked fatigability and irritability, loss of weight despite an excellent appetite, intermittent diarrhea, and intolerance to heat with excessive perspiration. She had noted a mass in the neck, gradually increasing in size, associated with some difficulty in swallowing, and shortness of breath after mild exercise. In addition, her menses, which had been regular since their onset at the age of thirteen, had become markedly irregular in the past two years.

Most symptoms were of one year's duration and progressing in severity, but the loss of weight was most marked in the preceding three months, during which time the patient estimated that she lost 60 lbs. She had been quite obese, weighing 235 lbs. at one time. On admission her weight was 165 lbs. She had received no previous medical care for this condition.

Physical examination revealed a well-developed and well-nourished patient, somewhat nervous, but not acutely ill. Bilateral exophthalmos was present, with definite lid lag and some difficulty of convergence of the eyes. The thyroid gland was enlarged bilaterally, soft and not nodular. No bruits were heard over the gland.

Examination of the heart revealed a thrusting apex beat, but no thrills were palpated. A grade 2 systolic murmur was heard best at the apex, and was transmitted to the left axilla. Fluoroscopy gave evidence of hypertrophy of the left ventricle.

The lungs were normal to percussion and auscultation. The abdomen was entirely normal; liver and spleen were not palpable. The extremities showed only a fine tremor of the hands, which were moist and warm. In view of the history and findings, a diagnosis of hyperthyroidism was made.

The results of laboratory procedures, done on admission, were as follows: RBC—3.82 million, Hb—57%, WBC—4,700 with 52% polys, 37% lymphocytes, 7% monocytes, and 3% eosinophiles. The urine was entirely normal. Blood chemistry showed an NPN

Received for publication November 25, 1946.

of 42, fasting glucose of 80. Blood serology was negative. The BMR was +62 per cent.

The patient was placed on a high caloric diet with vitamin supplements. Barbiturates were administered for sedation, and on May 6 the patient was started on Lugol's solution, Minims X, t.i.d. The advisability of using thiouracil in this case was fully considered, but it was concluded that the patient could be more quickly prepared for surgery, with less likelihood of a toxic reaction, by means of the Lugol's solution.

On this date, May 6, an EKG showed a sinus tachycardia and nonspecific ST-T changes, interpreted as being compatible with hyperthyroidism.

The patient responded well to this therapeutic regimen. She became much less nervous and irritable, and there was some slowing of the heart rate. The basal metabolism on May 11, five days after starting iodine, was plus 46 per cent, and by May 18 it had dropped to plus 26 per cent. However, she continued to lose weight during this period, and went from 165 lbs. on admission, to 152 lbs. on May 18.

On May 14, the patient complained of mild generalized pruritis, most marked on the neck. A mild acne of the face, back and chest had been noted on admission. Superimposed on this was a fine macular rash over the same areas, first noted on May 15. It faded within 24 hours, although mild pruritis persisted.

On May 18, the patient complained of a burning sensation and tearing of both eyes. During the evening she developed symptoms of coryza and a sore throat. Examination on the following morning, May 19, revealed a severe bilateral conjunctivitis, with marked dacryorrhea; there were also a profuse sialorrhea, and marked congestion of the nasal and pharyngeal mucosa. The tonsillar areas were covered with a thin white exudate. At this time the administration of the Lugol's solution was stopped because iodism was suspected.

On May 19, the patient's temperature ranged from 101–103.4° F. She continued to run an irregular fever, with a maximum of 104° F. until June 1.

Coincident with the rise in temperature and findings as above, the patient was started on penicillin, 20,000 U. every 3 hours. She was also given intravenous infusions of glucose in saline, and symptomatic therapy. Despite this, the condition became worse. Her conjunctivitis became purulent in type, and there were desquamating and bleeding lesions of the lips, buccal mucosa and tonsillar area, with marked cervical node enlargement. She further developed a discrete, reddish, maculopapular rash, generalized over the body and prominent on the hands and feet, with moderate pruritis. The diagnosis of iodine toxicity could now be established. However, the use of the barbiturates was also stopped.

By the evening of May 20, this sudden and fulminating toxic reaction had extended to the tracheobronchial tree. There were now signs of dyspnea, a dry cough, and diffuse wheezy and crackling rales in both lungs. The patient was placed in an oxygen tent. Her WBC at this time was 11,000.

The following day the WBC was 9,650 with 77% polys, 15% lymphs, 8% monocytes, and no eosinophiles. The RBC was 4.52 million with 84% Hb. Blood culture was negative. Throat cultures showed a variety of organisms, but were negative for diphtheria bacilli.

On May 22 the patient was toxic and exhausted, and markedly dyspneic. She was now coughing up huge amounts of a pale pink, watery sputum. Loud moist rales were heard in both lungs. In addition the patient now had frankly bloody urine, and the vaginal mucosa showed the same type of desquamating lesions as were apparent in the mouth.

A dermatological consultant saw the patient, and stated that the skin rash was of an erythema multiforme type, presumably on a toxic basis. Penicillin dosage was now stepped up to 40,000 U. every 3 hrs. The following day her general condition was es-

sentially unchanged. The skin lesions were larger, and covered her entire body, and were associated with marked tenderness of the palms of the hands and soles of the feet. Repeat blood serology was again negative.

Late that night, the patient had an episode of severe dyspnea, with inspiratory stridor and expectoration of profuse and tenaceous pink sputum. The trachea was repeatedly aspirated, and much thick mucous material was sucked up, with improvement in breathing.

The following day she was better, with less difficulty in breathing, although the profusely productive cough continued. An x-ray examination of the chest was negative. WBC was 7,400. However her RBC had fallen to 3.46 million, and Hb was 51%. Urinalysis showed a thickish, dark brown urine, with 4 plus albumen, many RBC and WBC, and many bacteria. There was no hemoglobinuria.

She continued to improve, and on May 26 the oxygen was discontinued. During the next few days she was very weak and exhausted. Only occasional rales were heard in the lungs. The skin lesions were still discrete, but covered with a dark brown crust, which pealed away to reveal a pink and firm skin. Her most distressing symptoms were pain and salivation due to the ulcerations of the mouth and lips.

A blood transfusion was given on May 26, after which there was progressive improvement, with a gradual clearing of all skin and mouth lesions. There was marked desquamation of the skin of the trunk, hands and feet, with the loss of seven nails on the hands and feet. By May 31 her only symptoms were extreme weakness and superficial ulcerations of the lips. During this entire episode, from May 18 to May 31, the patient lost 22 lbs. in weight.

On June 3 the patient was restarted on barbiturate therapy without any toxic reactions. On June 1, a repeat EKG showed similar findings to that taken on May 6, except that there was now T wave inversion in all leads. This record also was interpreted as being compatible with hyperthyroidism. The patient continued to regain her strength, although she had an unexplained episode of temperature elevation from June 14 to June 17. A BMR taken on June 19 was plus 56.2.

The following day, June 20, the patient was started on propylthiouracil (2), with an initial dose of 100 mg. daily which was later increased to 150 mg. This medication was continued, as a preoperative measure, until August 10.

The patient reacted satisfactorily to this new regimen. She gradually regained her weight, reaching 169 lbs. by Aug. 20. However, her BMR fluctuated between plus 23 and plus 58 per cent. The last preoperative report was plus 40 per cent Aug. 16. Despite this high reading, her general condition was excellent, with complete regression of all symptoms and gain in weight as stated.

The EKG now showed some extensive changes. July 12, all the ST-T deviations had disappeared; there was only a T3 inversion, and the record was interpreted as a borderline curve. On Aug. 5 and Aug. 30 the records were similar to those of July 12.

Propylthiouracil therapy was discontinued on Aug. 10, as an immediate preoperative measure, in order to lessen the friability of the thyroid gland at operation. Obviously, the use of iodine at this time was impossible. Subtotal thyroidectomy was performed Aug. 20. The patient made an uneventful recovery, and was asymptomatic when discharged Aug. 31. Her BMR on this date was plus 13 per cent.

The patient returned to the clinic for post-operative observation Sept. 3. At this time patch tests were performed to determine her cutaneous iodine sensitivity. Three gauze patches, each one inch square, were placed at six inch intervals over the patient's back.

Patch #1 was impregnated with Lugol's solution.

Patch #2 contained one-half strength tincture of iodine, U.S.P.

Patch #3 was a saline control.

On the same date, three control subjects were tested, using the same technic. All tests were read in 24 hours. None of the control patients showed any evidence of skin sensitivity to the iodine solutions beyond the mere staining of the skin.

However, our patient complained of pain over two of the patch areas, when she returned the following day. Examination revealed that the skin under both the iodine patches had undergone marked reaction. These areas of skin were raised, discolored, acutely tender with multiple vesicles. Upon perforation of the larger vesicles, a thin yellow fluid escaped. This reaction was interpreted as positive evidence of skin sensitivity to iodine. (See Fig. 1.)

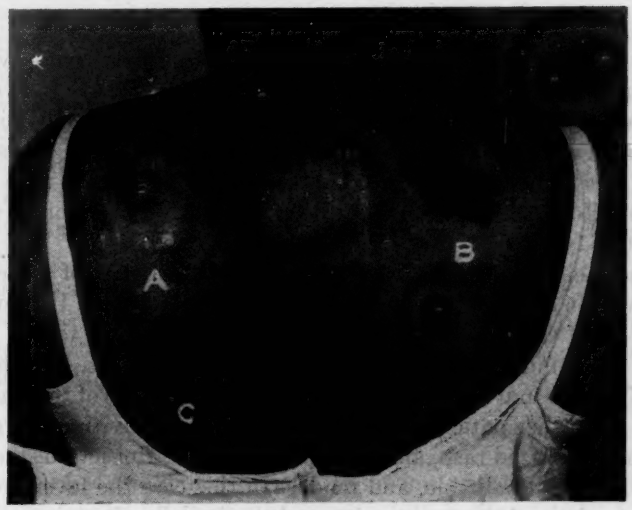

FIG. 1.—Patch test results with use of

A. Saline
B. A half strength tincture of iodine
C. Lugol's solution

Differential Diagnosis: The only condition that was considered in the differential diagnosis, in this patient, was Stevens-Johnson's disease. This is characterized by the skin lesions of erythema multiforme bullosum, with involvement of the mucous membranes (1-4-5-6-8-9-10-11). The clinical story is that of a sudden onset of symptoms; fever of 100–102° F., weakness, ophthalmia, and a generalized skin eruption occurring within 36–72 hours from the onset of symptoms. The lesions first appear macular in type, and rapidly progress to the formation of large vesicles. The most classical lesions are those about the lips and mouth. Here are found large bullous lesions which erupt, and produce sloughs. Genital lesions which simulate those in the mouth and conjunctival surfaces have been described by Edgar and Sylvester (5) ,and Ageloff (1). The average time for the disappearance of the eruption is two to three weeks. The oral lesions heal more slowly, because of secondary infection. No specific etiological agent has been identified with this disease. It has been suggested that these are cases of sensitivity to Vincent's infection, but this has not been proven. There is no laboratory or clinical proce-

dure which is specifically diagnostic for this disease. In reviewing the literature, it was found that no drugs were administered immediately prior to the onset of symptoms, in any of these cases.

In the present case, the diagnosis of Steven-Johnson's disease was excluded for the following reasons:

1) The outbreak of these lesions occurred during the course of iodine therapy.
2) Iodine sensitivity in this patient was confirmed by patch tests.
3) The skin eruption occurred within 24 hours from the onset of symptoms. These lesions were far more numerous than those described in Stevens-Johnson's disease.

DISCUSSION

Since Plummer's work in 1923, iodine has been used extensively in the management of toxic goiter. It is interesting to note that only two previous reports of iodism following the use of Lugol's solution are to be found in the literature. Barker and Wood (3), in 1940, reported seven cases of iodine toxicity in a series of 4,000 cases of hyperthyroidism which were treated at the Johns Hopkins Hospital. Guptill (7), in 1942, reported on an additional case of this type.

Of these eight cases, six were mild and all evidence of toxicity disappeared within one to two days after the drug was stopped. However, in two of these mild cases, a low-grade fever persisted for four to five weeks, although these individuals were asymptomatic. Two cases, both from the series of Barker and Wood, were severely toxic, and one of these terminated fatally. The other patient developed fever, conjunctivitis, enlarged lymph nodes, a generalized rash, and a definite jaundice. Her icterus index rose to 20, her liver was palpable, and tender. In this case the fever persisted for one week, the rash for two weeks, and the jaundice for one month. However, recovery was complete.

The fatal case was that of a Negro male, 56 years of age, who was started on Lugol's solution in a dose of 3 cc. daily. After two days of therapy, he developed a fever of 101.2° F. The dose of Lugol's was doubled in the hope that this might overcome the febrile response, but fever persisted and generalized pruritis developed. On the ninth day of treatment the drug was discontinued. Two days later, a saturated solution of potassium iodide was administered in its place, using 2 cc. the first day, and 3 cc. the second day. The patient responded with a fever of 104.2° F., a diffuse, reddish, macular eruption on the trunk, a hemorrhagic plaque on the palate, and coryza-like symptoms. The potassium iodide was discontinued but the eruption spread, the buccal mucosa became studded with petechiae, and the patient continued to be very sick.

Desquamating lesions of the tongue and palate appeared, and eight days after the potassium iodide was discontinued the patient became disoriented went into coma and died. Autopsy revealed that the mucosa of the mouth,

pharynx, larynx, trachea and bronchi were injected, and these mucous membranes were thinly coated with a grayish-white exudate. The liver, spleen, stomach and kidneys were hyperemic, with microscopically visible miliary, inflammatory, perivascular lesions.

Certain generalizations may be made on the basis of these nine cases of toxic response to Lugolization. The characteristic findings were as follows:

1) The first rise in temperature occurred between the second day and the eighteenth day after the start of Lugolization.
2) The maximum temperature ranged from 101° F. to 105° F.
3) A rash was present in six of the nine cases.
4) Five of these patients developed a conjunctivitis.
5) Seven of the patients had coryza-like symptoms.
6) Five of the patients had enlarged lymph nodes.
7) The WBC ranged from 5,000 to 12,200, but was above 10,000 in only 2 cases.
8) The original BMR determinations varied from plus 16 to plus 83 per cent.
9) Barbiturates were used in conjunction with Lugol's solution in all these cases. In most instances the barbiturates were continued or readministered after the Lugol's solution had been discontinued. None of these patients showed a further toxic response.

SUMMARY

1) A case of severe iodine toxicity following Lugolization is described. It was characterized by an abrupt onset, a fulminating course, high fever, diffuse and severe lesions of the skin and mucous membranes, coryza-like symptoms, enlarged lymph nodes, and only slight elevation of the W.B.C.

2) Following this episode, propylthiouracil was used in the further preoperative preparation of this patient; with satisfactory results and absence of toxic reaction.

REFERENCES

1. Ageloff, H. Erythema multiforme bullosum with involvement of mucous membranes of eyes and mouth (Stevens-Johnson's disease), *New England J. Med.* **223**: 217–219 (Aug. 8, 1940).
2. Astwood, E. B. and Vander Laan, W. P. Propythliouracil for hyperthyroidism. Bulletin New England Medical Center, 143–144 (June, 1946).
3. Barker, W. H. and Wood, W. B., Jr. Severe febrile iodism during treatment of hyperthyroidism. *J.A.M.A.* **114**: 1029–1038 (March 23, 1940).
4. Chick, F. E. and Witzberger, C. M. Erythema multiforme exudativum accompanying oral Vincent's infection. *Am. J. Dis. Child.* **55**: 573–578 (March, 1938).
5. Edgar, K. J. and Syverton, J. T. Erythema exudativum multiforme with ophthalmia and stomatitis. *J. Pediat.* **12**: 151–159 (Feb. 1938).

6. GINANDES, G. J. Eruptive fever with stomatitis and ophthalmia, atypical erythema exudativum multiforme (Stevens-Johnson's), *Am. J. Dis. Child.* **49**: 1148–1160 (May, 1935).
7. GUPTILL, P. Acute iodism during treatment of toxic goiter, *Surgery* **11**: 962–965 (June, 1942).
8. LEVY, A. T. Erythema multiforme bullosum with involvement of mucous membrane, of mouth (Stevens-Johnson's disease). *J. Am. Dent. A.* **30**: 287–288 (Feb. 1, 1943).
9. MURPHY, R. C., JR. An eruptive fever including the mouth and eyes (Stevens-Johnson's disease), *New England J. Med.* **230**: 69–71 (Jan. 20, 1944).
10. REED, J. Y. Stevens-Johnson's disease in edentulous mouth. *Bull. U. S. Army M. Dept.* **5**: 111–113 (Jan. 1946).
11. STEVENS, A. M. and JOHNSON, F. C. New eruptive fever associated with stomatitis and ophthalmia, *Am. J. Dis. Child.* **24**: 526–533 (Dec. 1922).

Letter to the Editor

To the Editor:

TREATMENT OF THIOURACIL AGRANULOCYTOSIS WITH STREPTOMYCIN

IN AGRANULOCYTOSIS the use of penicillin as a stop gap for infection, while the granulocytes are regenerating from their toxic effects, is well established. In complete agranulocytosis this regeneration usually begins within eight days. The thought occurred that streptomycin may be necessary in cases of this type which do not respond to penicillin. In the following patient with agranulocytic angina which followed the use of thiouracil, penicillin in large doses was not adequate and the patient still showed evidence of an infection on the sixth day of her illness. Gram negative organisms were found at this time on throat culture. Streptomycin[1] was substituted for penicillin. The patient recovered.

Agranulocytosis has numerous causes. The most common is a toxic reaction to some drug. At least twenty-one deaths from the use of thiouracil have been reported in the literature of agranulocytosis. One of the authors (B.S.) has observed five such cases, all of whom recovered. Two have been reported previously.[2] Since thiouracil has been such a frequent offender, propyl-thiouracil, a much less toxic drug, is now recommended in its place.

Harrison et al.[3] noted the disappearance of fever following the use of streptomycin for a period of eight days in a fatal case of agranulocytosis and aplastic anemia (amyloidemia[4]) following tridione. Streptomycin was discontinued and given again after a positive blood culture for B. Coli developed thirteen days later. Menorrhagia which was also present due to thrombocytopenia was treated by uterine packing which "contributed to the terminal infection and death."[5] Autopsy showed 96 per cent lymphocytes in the bone marrow. The following is a summary of the case history of one of our patients.

Mrs. E.S. was 30 years old and had one child. She was nervous, apprehensive and had slight exophthalmos. She had cramps and an urgent desire to defecate after each meal. Her teeth were in poor condition. The thyroid gland was diffusely enlarged to about twice the normal size. No bruit was noted. She had a marked tremor of the tongue and

---

[1] We are grateful to Dr. Charles S. Keefer and the Pfizer Company for release of the streptomycin used.

[2] Seligman, B. *Treatment of Agranulocytosis.* *J.A.M.A.* **129**: 1123 (1945).

[3] Harrison, F. H., *et al. Fatality Following Tridione.* *J.A.M.A.* **132**: 11 (1946).

[4] Seligman, B. *Amyeloidemia vs. Agranulocytosis.* *J.A.M.A.* **130**: 530 (1946).

[5] Dr. Harold Fink.

hands. Her weight was 103½ pounds, her pulse 140, her blood pressure 154/80 and her hemoglobin 75 per cent (Sahli). No signs of myocardial insufficiency other than tachycardia were noted. The basal metabolic rate was plus 44 per cent.

She was given 0.2 gram of thiouracil on June 25th. Thereafter, she was given 0.2 gram three times a day until August 4th when the drug was stopped because she devel-

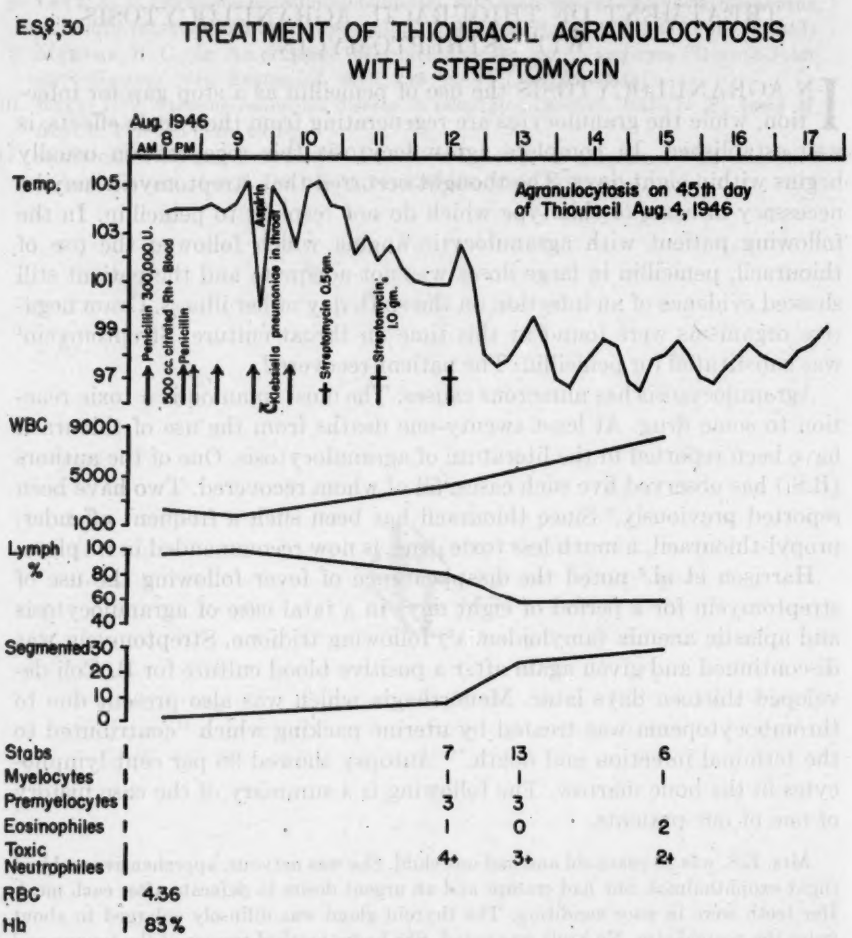
E.S. 9,30
TREATMENT OF THIOURACIL AGRANULOCYTOSIS WITH STREPTOMYCIN
Aug. 1946
AM 8 PM 9 10 11 12 13 14 15 16 17
Temp. 105 103 101 99 97
Agranulocytosis on 45th day of Thiouracil Aug. 4, 1946
Penicillin 300,000 U.
500 cc. citrated Rh+ Blood
Penicillin
Aspirin
Klebsiella pneumonica in throat
Streptomycin 0.5 gm.
Streptomycin 1.0 gm.
WBC 9000 5000 1000
Lymph % 100 80 60 40
Segmented 30 20 10 0
Stabs 1 7 13 6
Myelocytes 1 1 1 1
Premyelocytes 1 3 3
Eosinophiles 1 1 0 2
Toxic Neutrophiles 4+ 3+ 2+
RBC 1 4.36
Hb 1 83%

FIG. 1.

oped a sore throat. After one week of the thiouracil therapy she felt very much better, was less shaky, and slept and ate better. On July 26th her pulse was 84 and her weight 106 pounds. An interval blood count showed 6,200 white blood cells per cubic millimeter, 50 neutrophiles (5 non-segmented), 44 lymphocytes and one monocyte. Her hemoglobin was 84 per cent and her red blood count was 4,333,000 per cubic millimeter. No bone marrow studies were performed.

On August 4th, 1946 the throat was diffusely red. The next day a blood count showed 3,500 white blood cells per cubic millimeter with no polymorphonuclear cells. The temperature was 104 degrees by rectum and she received 300,000 units of penicillin in oil that night. On August 6th the throat showed edema of the uvula, tonsillar pillars and palate. 300,000 units of penicillin in oil was continued twice daily. On August 7th the temperature was 105.2 degrees and the throat showed small, white, necrotic areas on the uvula and tonsillar pillars. The anterior cervical glands were enlarged and firm. On August 7th (see chart) she was admitted to a private hospital and penicillin was given in a dose of 300,000 units three times during the day. Her temperature varied between 103.8 and 104° F. She was given one indirect transfusion of 500 cc. of RH positive blood. The blood count showed 2,200 white blood cells per cubic millimeter. Of the 99 cells counted only two were non-segmented polymorphonuclear cells. On August 9th she had a small abrasion of the lip which was not inflamed. The throat was red with a small vesicle on the uvula and slight edema of the tonsillar areas. She had gingivitis. A systolic murmur was noted at the apex. The chest was clear. The abdomen was soft. The liver edge was palpable and tender just below the costal margin. Her temperature varied between 104.2° and 105° F. Following fifteen grains of aspirin in divided doses the temperature dropped to 100° only to rise again. The next day the temperature fluctuated between 102.6° and 105.2° F. At this time the white blood count showed only 1,850 lymphocytes per cubic millimeter.

A smear of the throat on August 9, 1946 revealed gram negative bacteria which, on culture, proved to be Klebsiella pneumoniae (5). She was given one gram of streptomycin daily in eight divided doses for two and a half days. The temperature fell after the drug had been started on August 10th at 3:30 P.M. The throat began to clear. A burning throat pain disappeared on August 11 when she began to look, feel and eat well. The liver edge was not felt. On August 13th the skin was cold and heat applied. The patient had remained well except for slight weakness.

She was given as adjuvants 10 cc. of pentnucleotide daily and 5 cc. of crude liver extract intramuscularly. With each injection of pentnucleotide she felt weak and sweated. During the acute phase of her illness the patient showed, as do other people with agranulocytosis, red, slightly elevated areas at the site of all the hypodermic injections. In this patient the areas were not noted after August 13 when a peripheral smear showed 41 per cent granulocytes. She was also given 10 minims of Lugol's solution three times a day, multiple vitamins and tablets of liver and iron orally. One and one-half grains of phenobarbital was given nightly. Her mouth was washed with dilute hydrogen peroxide. She was allowed out of bed on August 15th and discharged from the hospital August 17th. Penicillin had been stopped when streptomycin was started.

While agranulocytosis may occasionally disappear spontaneously, no one will deny the effectiveness of antibiotics in most cases. Penicillin is not considered completely effective if local lesions are not healed and the temperature reaction persists after 48 hours. Secondary invaders may have come to the fore, as in this case, after the growth of penicillin sensitive organisms has been arrested. We feel that streptomycin may then be indicated.

BERNARD SELIGMAN
MORRIS WEINTROB
Brooklyn, New York
Nov. 17, 1946

Association Notice

The 29th annual meeting of the Association for the Study of Internal Secretions will be held Friday and Saturday, June 6th and 7th, 1947, in the Viking Room of Haddon Hall Hotel, Atlantic City, New Jersey, preceding the Centennial meeting of the American Medical Association.

For program see the February, 1947, issue of THIS JOURNAL.

Announcement of Awards

ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

The Association for the Study of Internal Secretions has just announced that the award provided by E. R. Squibb and Sons has been conferred on Doctors Carl F. and Gerty T. Cori of Washington University, the award furnished by the Ciba Pharmaceutical Company has been made to Doctor Choh Hao Li of the University of California, and the newly established fellowship of Ayerst, McKenna and Harrison, Limited, has been given to Doctor Samuel Dvoskin of Columbia University.

The Squibb Award to Dr. and Mrs. Cori was based on major contributions which they have made on the action of adrenalin, insulin, and the anterior pituitary and adrenal cortical hormones concerned with metabolism. They described the physiology of glucose and lactic acid in the liver, blood and muscles under the influence of adrenalin and insulin. They have identified and purified the enzymes concerned in glycogen formation and have accomplished the synthesis of glycogen in vitro. Some of their recent studies have demonstrated that the first step in glucose utilization (the hexokinase reaction), a step common to both glycogen formation and the oxidation of glucose, is inhibited by the anterior pituitary body. The release of this pituitary inhibition by insulin has afforded the first demonstration of an action of insulin apart from living tissue. This revelation of the quantitative biochemical relation of hormones and enzymes opens a new era in endocrine research.

Dr. Carl F. Cori was born in 1896. He received the degree of Doctor of Medicine from the German University, Prague, Austria in 1920. He served as assistant in the medical clinics in Prague and Vienna and as assistant in Pharmacology at Graz. He was biochemist at the State Institute for the Study of Malignant Diseases, Buffalo, 1922–1930, and Assistant Professor of Physiology at Buffalo, 1930–1931. From 1931 to 1941 he was Professor of Pharmacology, and from 1941 to 1946, Professor of Pharmacology and Biochemistry at Washington University. Since 1946 he has been Professor and Chairman of the Department of Biochemistry at Washington University. Dr. Gerty T. Cori was born in 1896 and received the degree of Doctor of Medicine at Prague in 1920. She was assistant pathologist and biochemist at the State Institute for the Study of Malignant Diseases in Buffalo from 1922 to 1931. Since 1931 she has been Research Associate in Pharmacology and Biochemistry at Washington University.

The Ciba Award to Doctor Li was given for his significant contributions

in the separation and study of hormones of protein nature and the isolation of the adrenocorticotropic and growth hormones in homogeneous and highly purified states. Dr. Li was born in Canton, China on April 21, 1912. He received the degree of Bachelor of Science from Nanking University in 1933 and the degree of Doctor of Philosophy from the University of California in 1938. From 1933 to 1935 he was an instructor at Nanking University. Since that time he has served at the University of California as Research Associate, 1938–1942, as Assistant Professor, 1942–1946, and since 1946 as Associate Professor of Experimental Biology.

Doctor Samuel Dvoskin was named to receive the first Ayerst, McKenna and Harrison Fellowship. He received both the Ph.D. and the M.D. degrees from Columbia University in 1945 and in his studies on the testis and thyroid has shown unusual promise as an investigator. He will continue his work on the thyroid gland and thyroid hormone assays under the direction of Dr. Robert Loeb.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor; D. A. McGINTY. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS.

GENERAL

LIMARZI, L. R., C. L. PIRANI, AND R. J. KULASAVAGE. The effect of thiouracil on leucemia with a clinicopathologic report of a case of chronic myeloid leucemia that developed an extreme neutropenic leucopenia. *J. Lab. & Clin. Med. 31*(4): 470–471 (1946).

Four patients with myeloid leucemia and one with lymphatic leucemia were treated with thiouracil in daily doses varying from 0.2 to 3.0 gm. for periods varying from eight to ninety days. The drug was without effect upon the course of the disease or the clinical condition in any of these patients. In one patient with myeloid leucemia, the white blood count was reduced from 440,000 to 1,900 cells per cubic mm. with the complete disappearance of all granulocytic elements from the peripheral blood except basophilic polymorphonuclear cells which represented 33 per cent of the leucocytes present. In this patient at autopsy, "the bone marrow showed numerous myeloblasts and lymphocytes, and a complete aplasia of mature and immature types of neutrophiles and eosinophiles" Thyroid hyperplasia was not produced in any of the five patients studied.—*T.H.McG.*

NICHOLSON, W. M. Emotional factors in obesity. *Am. J. Med. Sci. 211:* 443 (1946).

The author compared the effect on weight loss of psychotherapy without the use of calculated diets (38 cases), calculated diets only (35 cases), amphetamine sulphate only (10 cases), and thyroid substance only (10 cases) in obese patients who were 10 kg or more over their calculated ideal body weight. Except for women in the menopause age group, all other patients with endocrine disease, inactivity due to debilitating illness or encephalitis were excluded from the series. Unless a patient had maintained a weight loss of 5 kg or more for 1 year, or if any relapses occurred after a year, the experiment was considered to be a failure. The results were considered to be successful in 26 patients who received only psychotherapy, and in 9 patients who received only diet; all others were considered to be failures. The author concludes that all obese patients studied have some type of psychoneurosis in varying degrees, and hence that psychotherapy and re-establishment of proper dietary habits is essential for permanent weight reduction.—*E.C.R., Jr.*

ROBERTS, J. G. Disappearance of secondary sarcomatous deposits in the lungs after stilboestrol therapy. *Brit. J. 2:* 693 (1946).

A case of endothelioma originating from the capsule of the shoulder joint, developed cachexia 18 months after fore-quarter amputation. X-ray examination showed multiple metastases in the lungs. Stilbestrol treatment was instituted, first by injection and later by mouth. She regained weight and lungs became radiologically normal. Patient is in excellent health 3 years and 9 months after amputation and 2 years, 1 month after beginning stilbestrol therapy.—*L.T.S.*

GONADS

BLOCK, F. B. Ovarian Tumors. *Am. J. Med. Sci. 212:* 738 (1946).

The author reviews recent reports in the literature from a clinical point of view. The subjects treated include: granulosa-cell tumor, theca-cell tumors, arrhenoblastoma, dysgerminoma, Brenner tumor, adrenal rest tumor, teratoma, carcinoma, adenoacanthoma, Krukenberg's tumor, and fibroma.—*E.C.R., Jr.*

GREENHILL, M. H. A psychosomatic evaluation of the psychiatric and endocrinological factors in the menopause. *South. Med. Jour. 39*(10): 786–794 (1946).

In an investigation of the psychiatric and endocrinologic factors observed at the menopause, the author found that the psychiatric states could be associated with the menopause but were rarely a symptom of hypo-ovarianism. The evidence presented showed that the psychoneurosis never began with the menopause. The anxiety neurosis, hysteria, phobic states and compulsive-obsessive neurosis observed during the climacteric usually had been observed some time prior to the period of hypo-ovarianism. Twenty-five per cent of the patients who had psychoneurosis at the menopause had merely experienced a continuation of the symptoms which they had exhibited prior to that time. Involutional melancholia, tension states and reactive depressions were the most common psychiatric disorders observed at the climacteric. A comparison of the effectiveness of estrogens in the psychiatric patients and in those with the usual menopausal autonomic lability showed hormone therapy to be effective in only 3 per cent of the psychiatric patients as compared to alleviation of symptoms in 62 per cent of the women exhibiting autonomic lability. In concluding the author stated that there was no justification for the term 'menopausal syndrome' if it implied the presence of a psychiatric disorder in its definition.—*H.S.K.*

KARNAKY, K. J. Hydrogen ion concentration of the senile vaginal mucosa before and after estrogenic therapy. *South. Med. Jour. 39*(11): 906–907 (1946).

Determinations of the hydrogen ion concentration of the senile vagina were made before and after estrogenic therapy. The average pH of the normal vagina varied from 4.10 to 4.14, depending upon the area examined. The variation in the pH of the senile vaginal mucosa ranged from 6.27 to 6.42. Estrogenic substances lowered the pH of the senile vaginal mucous membrane. Stilbestrol, 0.5 mg. per day for 23 days, increased the hydrogen ion concentration more than ethinyl estradiol administered in daily doses of 0.09 mg.—*H.S.K.*

MASSON, G. The spermatogenic activity of Δ^5-pregnenolone and of its esters. *Am. J. Med. Sci. 212:* 1 (1946).

Spermatogenic activity of steroid compounds is defined by the author as the ability of these substances to prevent testicular atrophy following hypophysectomy, or treatment with estradiol, small doses of testosterone or non-specific agents. Steroids are divided into 2 groups: those which are capable of restoring spermatogenesis in a testis previously rendered atrophic by hypophysectomy (compounds of the testosterone and androstenediol type), and those which do not possess this property (compounds of the progesterone type). The author has investigated the nature of the spermatogenic activity of Δ^5-pregnenolone and of its acetate, propionate and benzoate on three groups of hypophysectomized rats, on two groups of rats given estradiol before or during pregnenolone treatment, and two groups of rats given estradiol before testosterone treatment. The results were evaluated in terms of the weight of the testes, the weight of the seminal vesicles, the weight of the prostate, the weight of the adrenals, and the evidence of spermatogenesis from histological examination. It was shown that testosterone accelerates, while pregnenolone inhibits the regeneration of the atrophic testis. On the basis of these results the author classifies testosterone as an *active* spermatogenic compound which directly stimulates the proliferation of the germinal epithelium, and pregnenolone as a *passive* spermatogenic agent, whose action consists merely in protecting and maintaining the testis in the condition in which it is at the commencement of treatment. The author states that this classification may serve as a basis for the rational selection of gonadotrophic steroids for clinical use. The steroids which belong to the testosterone and androstenediol type should be used only when the testis is already damaged, because, in the case of almost normal testes, there is danger of causing Leydig cell atrophy by such treatment, and this may represent a greater evil than the diminution in the spermatogenesis. Conversely pregnenolone should be used only if a comparatively normal testis is to be protected against subsequent damage. With this compound there is no reason to fear any unpleasant side-effects since at the daily dose of 10 mg. it is practically devoid of folliculoid, testoid, and corticoid activities and possesses only weak luteoid properties. The combination of testosterone and pregnenolone is suggested for the treatment of eunuchoidism without the danger of producing testis atrophy. —*E.C.R., Jr.*

TEILUM, GUNNAR. Gonocytoma. Homologous ovarian and testicular tumors. I. *Acta Path. et Microbiol. Scandinav. 23*(3): 242–251 (1946).

A detailed documentation is given of the previously demonstrated morphological congruity (Teilum, 1943) between the ovarian tumor misinterpreted by Schiller as mesonephroma and a most often adenopapilliferous, solid or cystic (sometimes teratoid), tumor of the testis. On the basis of the continuity demonstrated between this tumor form and, on the one side, seminoma (dysgerminoma), and on the other side, chorioma, the writer sets up two homologous tumor series in the ovary and testis, between which the present tumor is entered as an intermediate form.

Histogenetically, this entire group of tumors (gonocytomas) is characterized by their origin from early stages of the germ cells in the testis or from homologous remnants of the medullary cords in the ovary. In the ovary, thus not only the dysgerminoma but also the intermediate form (gonocytoma II) and the primary chorioma (gonocytoma III) appear as a morphogenetically defined group originating from a particular testicular

anlage. In connection with the critical evaluation of the term "mesonephroma ovarii," the description is given of a case of malignant ovarian tumor, which, in contrast to the true tumor from described by Schiller, has to be looked upon as a true mesonephroma.—*Author's Summary.*

TEILUM, GUNNAR. Arrhenoblastoma—Androblastoma. Homologous ovarian and testicular tumors. II. *Acta Path. et Microbiol. Scandinav. 23*(3): 251–264 (1946).

In connection with previous papers on homologous tumors of the ovary and testis, a case of feminizing testicular tumor is described showing complete morphological congruity with the virilizing arrhenoblastoma of the ovary described by Robert Meyer. The patient was a man, aged 53. The tumor had persisted for 30 years and had increased further during the last year. In the past 3 years there had been impotence and during the last year increasing gynecomastia. After the removal of the tumor, the gynecomastia began to subside. On the cut surface the tumor was intensely yellow in color. Histologically, a considerable lipoid content was demonstrated. Thus the previously established testicular androblastoma (homologous with Meyers arrhenoblastoma of the ovary) is extended to include hormone-producing tumors showing all the differentiating stages known from the arrhenoblastoma. The hitherto unknown occurrence of this form of tumor demonstrates the correctness of Meyer's view concerning arrhenoblastoma of the ovary.

Further, a gradual transition is demonstrated from tumor tissue of the androblastoma type to clear-cut lipoid cell tumor which shows morphological congruity with the virilizing lipoid-containing ovarian tumors generally described as "luteoma," "adrenal tumors," "ovarian hypernephroma" and "folliculome lipidique." Accordingly, such ovarian tumors are now to be looked on as a particularly lipoidal form of ovarian arrhenoblastoma. In addition diffuse forms of tumors containing no lipoid occur in the ovary as well as the testis which are to be considered as variants within the androblastoma series and may have a relative virilizing and feminizing effect. They are tumors with more or less pronounced differentiation in the direction of testicular interstitial-cell tumors and a homologous extraglandular, interstitial-cell tumor of the ovary.

The demonstrated homologous tumor series—respectively the seminoma (dysgerminoma) and androblastoma (arrhenoblastoma) series that may be encountered in the testis as well as the ovary in all forms of differentiation, are set up as the basis of a classification comprising both tumors of the testis and the "testicular" tumors of the ovary in keeping with the histogenetic and biological aspects. This further affords a far more clear-cut morphological differentiation of such ovarian tumors from other particular forms, e.g., the granulosa cell tumors.—*Author's Summary.*

WEAVER, J. D. Estrogenic hormones, often only a psychotherapeutic agent. *South. Med. Jour. 39*(7): 581–585 (1946).

The use of estrogens was decried and the reported beneficial effects usually observed after estrogenic therapy are considered merely on the basis of the psychotherapeutic action of the drug. The menopausal syndrome was described as a purely psychic reaction with its inception based upon the earlier conditioning of the patient. Data presented were slim, philosophical condemnation extensive, and abstinence from general use of estrogens was advocated. No indications for estrogens were discussed.—*H.S.K.*

PANCREAS

BRIGGS, A. P. Some observations on severe diabetic ketosis treated with glucose and insulin. *J. Lab. & Clin. Med. 31*(11): 1244–1248 (1946).

Seven diabetic patients have been observed under treatment for severe ketosis. Quantitative estimations have been made of the free acetone and total acetone bodies of the blood and urine, and of the blood sugar. Qualitative determinations for the acetone bodies and sugar of the urine have been performed. The data obtained confirm the fact that the free acetone of the blood represents a substantial and reasonably constant (20 to 32 per cent) portion of the total acetone bodies of the blood. The total acetone bodies of the urine will not rise proportionately to those in the blood in cases with disturbances of renal function. The ferric chloride test for diacetic acid in the urine is often negative, even in the presence of large amounts of ketone bodies. "Too much reliance should not be placed on tests for diacetic acid in the urine in the diagnosis of diabetic coma." The author favors the administration of glucose to the diabetic in coma "in quantities equivalent to at least half of the caloric requirements." He believes this is well justified therapy because (1) the patient in diabetic coma needs carbohydrate and (2) the administration of glucose lessens the chance of hypoglycemia. He recognizes the fact that the administration of glucose interferes with the use of blood and urine sugar levels as an index of the insulin requirement, but suggests that the tests for ketosis described in the paper may be satisfactorily substituted. In addition, the determination of plasma bicarbonate may be helpful, as suggested by others.—*T.H.McG.*

CONNOR, J. F., AND F. W. REYNOLDS. The two-dose dextrose tolerance test in the diagnosis of diabetes mellitus. *J. Lab. & Clin. Med. 31*(10): 1121–1128 (1946).

A statistical analysis has been made of the two-dose dextrose tolerance test performed on 26 normal persons, 82 with diabetes mellitus, 7 with renal glycosuria and 6 individuals in whom a disturbance of carbohydrate metabolism was questionable. The technique for carrying out the tests was similar to that employed by Rose and Exton except that all subjects irrespective of weight received 100 gm. of glucose as a 15 per cent solution divided into two equal portions given at the 0 and ½ hour periods respectively. Moreover, determination of the blood and urine sugar was made at the end of 2 hours in each individual. Of the 82 diabetic subjects, 22 required insulin; 49 were regulated satisfactorily without insulin; and 11 needed insulin in the early portion of their treatment but were later able to discontinue it. It is not clear from the text whether any of the tests were performed prior to regulation of the diabetes, but the assumption is that all of the subjects were reasonably well controlled when the study was begun. Of all the data obtained, the authors believe "the height of the one-hour blood sugar is the most reliable criterion for differentiating the normal person from the diabetic patient." They found that normal subjects gave readings at one hour of 150 mg. of glucose per 100 cc. or less, and that diabetic subjects showed 170 mg. or more of dextrose per 100 cc. of blood. The values for doubtful cases fell between these two figures. The two-hour reading was the next most reliable determination, and even if not done in all instances, should always be carried out in the doubtful case. At two hours, normal subjects had a blood sugar of 125 mg. or less per 100 cc. of blood, while values for the diabetic were 135 mg. or more per 100 cc. The one-half hour reading afforded little or no information, and from the viewpoint of the authors "may well be deleted from the procedure." A high

one-hour reading with a normal two-hour reading may be indicative of an excessively rapid absorption of dextrose; conversely, a normal one-hour figure with a high two-hour value may represent a delay in the emptying time of the stomach. As is the case with any other laboratory procedure, too much reliance should not be placed upon the results of the test alone. It should be interpreted in the light of all the clinical data.—*T.H.McG.*

DUMM, R. M., AND R. A. SHIPLEY. The simple estimation of blood ketones in diabetic acidosis. *J. Lab. & Clin. Med. 31*(10): 1162–1163 (1946).

An especially prepared nitroprusside powder has been used for the detection of acetone in body fluids. A single drop of the fluid to be tested is added to a pinch of the powder, 5 mm. in diameter, on white filter paper. When the reaction is positive a violet color reaction promptly occurs which is absorbed into the paper and may last for several hours. A drop of serum from blood containing a total of approximately 10 mg. of total acetone bodies per 100 cc. will give a positive reaction. Therefore, by a series of dilutions of the serum, it is possible to determine quickly the blood levels for acetone bodies within an accuracy of plus or minus 10 mg. per 100 cc. The authors have found their estimations with the method to check well with microchemical determinations within the range over which the method has been applied, viz. from 0 to 100 mg. of total acetone bodies per 100 cc. The method has been found particularly useful in (1) the routine management of diabetic coma; (2) the prompt recognition of surgical complications simulating coma in the diabetic as contrasted with coma itself and (3) the differentiation of minimal ketonuria due to minimal ketonemia from minimal ketonuria with depressed renal function and severe ketonemia.—*T.H.McG.*

ENGELHARDT, H. T., AND J. P. MELVIN, JR. The management of diabetes mellitus during pregnancy. *South. Med. Jour. 39*(9): 734–737 (1946).

Despite the fall in maternal mortality observed in diabetic pregnant women treated with insulin, infant mortality in these individuals has remained consistently high. Of 1490 diabetic women examined, 23 or 1.6 per cent, were obstetric cases. In this latter group, two patients were admitted to the hospital in coma, one of whom died, and three were seen in severe acidosis. There were only two cases of polyhydramnios, and a fetal mortality of 47 per cent was observed. The treatment of the pregnant diabetic and the physiologic changes in carbohydrate tolerance during pregnancy were classified according to the trimester the patient was examined. In the first trimester, the lowered renal threshold and decreased glucose tolerance resulted in increased insulin requirements. Little or no change was observed in carbohydrate tolerance or insulin requirements in the second trimester. The third trimester was characterized by sudden changes in carbohydrate tolerance. Therefore no dogmatic routine could be prescribed in this stage. The same dietary and weight restrictions observed in normal pregnant women should be ascribed to in pregnant diabetics. The authors advocated the use of the preconception dose of protamine zinc insulin and advised control of significant glycosuria by the use of crystalline insulin. All patients were delivered per vaginam. The authors did not attempt to explain the difference between the effect of insulin in reducing the maternal mortality rate and its failure to prevent fetal mortality over that seen in pregnant diabetics in the pre-insulin days.—*H.S.K.*

FISHER, A. E., AND HENRY BOLGER. Behavior and psychologic problems of young diabetic patients. *Arch. Int. Med. 78:* 711 (1946).

The problems which arose in 43 young diabetic patients from childhood through adolescence to maturity have been analyzed. Each patient had been observed for at least ten years. The type of home, its economic security and the contacts at school and in social life, all had especial influence on the reaction of the diabetic child to his disease. Specific problems of childhood became less disturbing with the onset of maturity. During adolescence, problems relating to vocation and marriage appeared. Maturity usually brought about improvement in behavior, with the desire for independence being its outstanding characteristic. Marriage for the young diabetic person was difficult, especially for the young women. However, most of the marriages have been happy ones. The specific effects of diabetes on behavior were unrelated to the age of onset, the duration or the severity of the disease. Diabetic regimentation, while necessary, at first produced behavior difficulties. The immediate and the more remote or cumulative effects of hypoglycemia on the brain were considered to be potentially serious. Psychopathic behavior in a serious form was exhibited in 3 patients; other minor behavior disturbances were frequent. Patients in the better economic group and with better home environment had higher intelligence quotients and made more satisfactory adjustments to diabetes.—*I.B.*

GABRILOVE, J. L. Chloride excretion during glycosuria in patients with diabetes. *J. Clin. Investigation 25*(2): 256–260 (1946).

Seven diabetic patients without ketosis were given diets containing from 2 to 4 grams of salt daily. While fully controlled from a diabetic viewpoint, the excretion of chloride on such a diet was averaged for a control period of seven days. Glycosuria was then induced by administering additional carbohydrate, by the withdrawal of insulin or by a combination of these procedures. There was no increase in the chloride excretion during glycosuria without ketosis even though the glycosuria was marked in degree and prolonged many days.—*T.H.McG.*

GOLDSTEIN, N. P., M. JACOBSON, I. R. TELFORD, AND J. F. ROE. Studies of pancreatic function. III. The effect of ligation of the pancreatic ducts upon the amylase and lipidase content of the blood. *J. Lab. & Clin. Med. 31*(9): 999 (1946).

Values for the amylase and lipidase of the blood serum were determined before and at periodic intervals for 8 months following the ligation of the pancreatic ducts of four cats. The usual immediate increase of these substances in the serum was observed postoperatively. At the one and two-month intervals all the animals showed values for amylase definitely below the control figures. Variations in the lipidase content of the serum were less well marked, but a "recognizable decrease" could be observed 3 months postoperatively. From the third month onward, there was a gradual increase in the value for both substances, and by the end of the eighth month the serum concentrations for both were normal. In connection with these changes, it is of considerable interest to note that the pancreas of one animal was "completely atrophic"; that little acinar tissue was recognizable in two, while the fourth showed some "normal areas of acinar tissue."

Despite this variation in the histological picture, the behavior of serum amylase and lipidase was quite similar in all four of the cats. The authors conclude that the subsequent return to normal of the values for serum amylase and lipidase were due to extrapancreatic factors. Moreover, the results of their experiments led them to believe that the determination of serum lipidase is as nonspecific as the amylase test in the diagnosis of chronic pancreatic disease.—*T.H.McG*

KIMBLE, M. S., O. A. GERMEK, AND E. L. SEVRINGHAUS. Vitamin A and carotene metabolism in the diabetic as reflected by blood levels. *Am. J. Med. Sci. 212:* 574 (1946).

Plasma vitamin A and carotene levels were determined by dependable methods in 116 unselected diabetics. All possible types of deviation from the normal range in vitamin A: carotene relationship were observed. Values for one or both substances outside the normal range for the appropriate sex were found at hospital admission in the blood of 49% of the 59 males and 47% of the 57 female patients. The predominant type of deviation in the series as a whole was low vitamin A: low carotene. This was particularly noticeable among older patients and patients with infection. Least prominent of any trend was that toward high carotene with deficient vitamin A, an alteration that has been widely assumed to be characteristic of diabetes and that has been rationalized as resulting from a defect in the diabetic organism's ability to derive vitamin A from its pro-vitamin, carotene. Relatively uncommon in the series was the so-called diabetic carotenemia, considered without regard for the accompanying vitamin A level. From analysis of the individual cases in the light of present knowledge of the facts that can alter vitamin A supplies, availability, reserves, use, and the resultant blood levels, it is evident that there is no type of aberrant blood picture found in this series of diabetics that cannot be explained by considerations not necessarily peculiar to the diabetic, especially if general nutritional failure (less frequent than it used to be among diabetics) is included as a possible cause for inefficient use of ingested carotene.—*E.C.R., Jr.*

LANGNER, P. H., M. J. ROMANSKY, AND E. D. ROBIN. The fallacy of the Exton-Rose glucose tolerance test. *Am. J. Med. Sci. 212:* 466 (1946).

The authors contend that the Exton-Rose 2-dose, 1-hour, glucose tolerance test is based upon a physiologic misconception. They believe that in arriving at the conclusion that a second 50 gm. dose of glucose would have any appreciable effect upon the blood sugar curve in the short space of ½ hour, Exton and Rose failed to take into consideration certain physiologic facts: 1) the rate of absorption of glucose from the gastro-intestinal tract, 2) its rate of utilization, and 3) the natural shape of a glucose tolerance curve after giving 100 gm. of glucose, whether it is given in 1 dose or in divided doses of 50 gm., at ½ hour intervals. They cite evidence which indicates that the second dose of 50 gm. adds glucose at a time when there is still an excess in the upper intestinal tract. It would seem pointless to give a second dose of glucose at the height of the blood sugar curve, since in a normal individual the curve would fall whether a second dose were given or not given. In a diabetic the curve would continue to rise whether 1 initial dose or 2 doses at ½ hour intervals were given. Therefore, any difference in the effect which the administration of 1 dose of 100 gm. or 2 doses of 5 gm. each would have upon the blood sugar curve would not be manifested during the first hour or during the duration of the entire Exton-Rose test. The fact that the body requires 1 hour to dispose of 25 gm. of glucose given intravenously, thereby producing the maximum stimulus, makes it seem

unlikely that the disposal of an oral dose of 50 gm. could occur in ½ hour and any appreciable response be manifested to a second dose of 50 gm. The results of a series of well-controlled glucose tolerance tests are presented to support the contention that after giving 100 gm. of glucose in 1 initial dose the blood glucose curve is essentially the same as that obtained after giving 100 gm. in 2 divided doses of 50 gm. initially and 50 gm. at ½ hour (the Exton-Rose procedure). They point out that the interruption of the oral glucose tolerance test at 1 hour and the consequent use of the peak value as the criterion is much less accurate than the use of the 2 or 3 hour value of the glucose tolerance curve. They conclude that the Exton-Rose test is based on an hypothesis that is physiologically unsound, that the test is not a physiological entity, and that it is not basically different from the 1-dose glucose tolerance test.—*E.C.R., Jr.*

LAZAROW, A., AND S. L. PALAY. The production and course of alloxan diabetes in the rat. *J. Lab. & Clin. Med. 31*(9): 1004–1015 (1946).

The purpose of this work was to develop a method by which diabetes could be consistently produced in the rat. In all, 77 rats were injected with alloxan either intraperitoneally or intravenously. The variability of results obtained by intraperitoneal administration was ascribed to the "highly variable factor of destruction," which is minimized when the drug is given rapidly by the intravenous route. An injection of 40 mg. per kg. intravenously produced about the same degree of diabetes as a dose of 200 mg. per kg. intraperitoneally, and did so much more consistently. Dosages of from 50 to 200 mg. per kg. intraperitoneally and of from 15 to 100 mg. per kg. intravenously were tried. At the highest dosage level used intraperitoneally, 75 per cent of the animals developed diabetes, but appreciable renal damage was invariably present. Following the intravenous injection of alloxan, there was an initial hyperglycemia lasting three hours or more, followed by a very short period of hypoglycemia and finally a permanent hyperglycemic phase, usually reached by the end of 48 hours. All animals responded in the above fashion when 40 or more mg. per kg. were given intravenously, whereas only 75 per cent responded similarly to the largest doses (200 mg./kg.) intraperitoneally. The severity of the blood sugar responses varied directly with the size of the dose of alloxan. Renal damage was not significant in animals receiving intravenously a dose of 40 mg. or less per kg. This is in contrast to the fact that azotemia and renal damage were invariably present when the same degree and severity of diabetes was caused by the intraperitoneal injection of 200 mg. per kg. As a rule, by the use of a single intravenous dose of 40 mg. per kg. of body weight, it was possible to develop a moderately severe to severe diabetes in which the values for blood sugar continued to rise gradually to attain a height of from 400 to 600 mg. per 100 cc. within several weeks. The authors believe that the intravenous use of alloxan affords a dependable way to produce experimental diabetes consistently, and feel that the administration of a dose of 40 mg. per kg. of body weight will be followed by damage to the pancreas resulting in the loss of function of the beta cells without serious lesions in the liver or kidney.—*T.H.McG.*

PAGE, R. C., AND E. H. LANG. Study of absorption from crystalline insulin pellets and solutions at various sites in rabbits. *J. Lab. & Clin. Med. 31*(10): 1144–1147 (1946).

Hand-compressed pellets of crystalline zinc insulin varying in size from 2.9 to 6.5 mg. with a potency of 25.89 units per milligram were implanted subcutaneously, intramuscularly, or intrasplenically into rabbits. Blood sugar values were determined just

prior to the implantation and at 4, 5, 24 and 30 hours thereafter. All control animals survived the 30 hour period of observation. Eighty per cent of the animals with subcutaneous implants died of insulin shock within 24 hours, whereas 40 per cent of those with the intramuscular and intrasplenic implants, respectively, had succumbed in a similar manner within the same period of time. At 30 hours, the surviving animals of the subcutaneously implanted group showed normal values for glucose in the blood. For the subcutaneous and intramuscular routes of implantation, the most pronounced hypoglycemic effect was observed between the 4th and the 5th hours and had disappeared in the surviving animals by the end of the 24 hour period. In the case of the intrasplenic implantations, the insulin effect was much more prolonged with an average value for blood glucose at 24 hours in the 6 surviving animals of 51 mg. per 100 cc. The more rapid and intense hypoglycemia produced by the subcutaneous implantation was attributed by the authors to mechanical factors causing a more rapid breakdown of the pellets. This conclusion seemed all the more valid in view of the fact that no significant differences in the action of insulin in rabbits between intramuscular and subcutaneous injections of watery solutions could be demonstrated with regard to the speed of onset and depth of hypoglycemia. Despite the fact that the absorption of insulin from the splenic implants closely followed the route normally taken by endogenous insulin after its release from the pancreas, the authors could detect "no appreciable hepatic regulation."—*T.H.McG.*

REVENO, W. S. Thiouracil effect in diabetes mellitus complicated by hyperthyroidism. *Am. J. Med. Sci. 211:* 174 (1946).

According to the author, diabetes mellitus and hyperthyroidism occur together in two different combinations: (1) secondary hyperthyroidism (toxic adenoma) which becomes manifest after the diabetes mellitus has appeared, and 2) primary hyperthyroidism (exophthalmic or toxic diffuse goiter) which antedates the diabetes mellitus in appearance. The author treated 6 patients with this combination of disorders with thiouracil and obtained improved control of the diabetes in the 4 of the secondary type; the other two patients failed to respond favorably or became worse. Of the 13 patients previously reported in the literature the 4 that responded favorably were the only cases of the secondary type. The author believes that thiouracil is as effective as thyroidectomy in diabetics who have secondary hyperthyroidism, but that in those who have primary hyperthyroidism or exophthalmic goiter thiouracil exerts little favorable influence on the control of the diabetes although it does control the manifestations of thyrotoxicosis.—*E.C.R., Jr.*